Exploring Cognitive and Behavioural Factors in Irritable Bowel Syndrome

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Exploring Cognitive and Behavioural Factors in Irritable Bowel Syndrome

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Abstract

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterised by altered stool frequency and/or consistency in addition to abdominal pain. There are four bowel pattern subtypes in IBS: diarrhoea predominant IBS (IBS-D), constipation predominant IBS (IBS-C), alternating bowel habit IBS (IBS-A) and unclassified IBS (IBS-U). IBS is a biopsychosocial syndrome and the predominant psychological treatment is cognitive behavioural therapy (CBT). The objectives of this PhD were (1) to assess whether cognitive and behavioural factors were mediators of treatment effect on the outcomes of symptom severity and work and social adjustment/quality of life, and (2) to identify whether cognitive and behavioural factors were associated with IBS bowel pattern subtypes. Two studies (studies one and two) were conducted to assess objective one, and two studies (studies three and four) were conducted to address objective two. Two data samples were used for analyses conducted in this thesis. Data set 1 was from a previously conducted randomised controlled trial (RCT) including IBS participants meeting Rome I criteria with a GP diagnosis of IBS. Data set 2 was from a new RCT including refractory IBS participants meeting Rome III criteria with a GP diagnosis of IBS.

A systematic review (study one) of mediation analysis conducted in the context of psychological interventions for IBS returned nine studies. The results suggested that illness-related cognitions were important mediators of treatment effect for the outcomes of symptom severity and quality of life. Gastrointestinal (GI) specific anxiety was found to be a mediator more often than general anxiety was. Only two studies assessed the mediating role of behaviours. The study assessing GI related behaviours found them to significantly mediate treatment effect, but the other study assessing general all-or-nothing behaviours did not find significant mediation. Study two utilised data set 1. It assessed simple and sequential mediation models in the context of an RCT assessing the effect of CBT + mebeverine to mebeverine alone on symptom severity and work and social adjustment in IBS participants (n=148). Simple mediation models found that general anxiety, GI related cognitions and GI safety behaviours mediated treatment effect on both outcomes. GI avoidance behaviour was not found to be a significant mediator. Sequential mediation models indicated that change in GI cognitions and GI safety behaviours preceded a reduction in general anxiety, and these sequential paths significantly mediated treatment effect on both outcomes.

Study three and four assessed differences in GI cognitions, GI safety behaviours, GI avoidance behaviours, general anxiety, work and social adjustment and symptom severity between IBS bowel pattern subtypes (IBS-A, IBS-C and IBS-D) using ANOVAs. IBS-U was excluded due to a disproportionately low number of participants in both studies classified as IBS-U. There was a significantly higher level of avoidance behaviours in the IBS-A and IBS-D subtypes than in IBS-C found in both studies. IBS-A was also found to have significantly higher levels of safety behaviours than IBS-D in both studies. However, in study three those with IBS-A also had significantly higher safety behaviours than those with IBS-C, whereas in study four, those with IBS-C (along with IBS-A) had significantly higher safety behaviours than those with IBS-D. In study three there was a non-significant trend towards a greater level of unhelpful GI related cognitions in those with IBS-D compared to the other two subtypes and this was found to be a significant difference in study four.

Together the results of this thesis suggest that cognitive and behavioural factors are important treatment mechanisms in IBS as well as potentially modifiable factors to help treatment targeting for particular IBS subtypes. Future directions for research should involve (1) mediation analysis including all process variables as identified by the CBT models of IBS (2) cluster analysis to identify subgroups in IBS classified by psychological factors in addition to bowel pattern predominance (3) assessment of moderated mediation to assess whether treatment mechanisms vary depending on subgroup membership in IBS.

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Abbreviations

Abbreviation	Meaning
AB	Avoidance behaviour
ACC	Anterior cingulate cortex
ACTIB	Assessing cognitive therapy in irritable bowel
ACTH	Adrenocorticotropic hormone
AIC	Akaike's information criterion
ANOVA	Analysis of variance
ANS	Autonomic nervous system
BGA	Brain gut axis
BIC	Bayesian information criterion
CB	Cognitive behavioural
CBT	Cognitive behavioural therapy
CBT-IE	Interoceptive exposure based cognitive behavioural therapy
CFI	Comparative fit index
CNS	Central nervous system
CRH	Corticotropin releasing hormone
CRP	C-reactive protein
CSFBD	Cognitive scale for functional bowel disorders
DSM-V	Diagnostic statistical manual 5
ENS	Enteric nervous system
ESR	Erythocyte sedimentation rate
FBC	Full blood count
FGID	Functional gastrointestinal disorder
GDH	Gut directed hypnotherapy
GI	Gastrointestinal
GP	General practitioner
GSA	Gastrointestinal specific anxiety
GSRS	Gastrointestinal symptom rating scale
HADS	Hospital anxiety and depression scale
HCP	Healthcare practitioner
HPA	Hypothalamic pituitary-adrenal axis
HT	Hypnotherapy
IAPT	Increasing access to psychological therapies
IBS	Irritable bowel syndrome
IBS-A	Alternating irritable bowel syndrome
IBS-BRQ	Irritable bowel syndrome behavioural responses questionnaire
IBS-C	Constipation predominant irritable bowel syndrome
IBS-D	Diarrhoea predominant irritable bowel syndrome
IBS- SSS	Irritable bowel syndrome severity scoring system
IBS-U	Unclassified irritable bowel syndrome
IPT	Interpersonal therapy
IPQ	Illness perception questionnaire
LCA	Latent class analysis
MD	Mean difference
MUS/LTC	Medically unexplained symptoms/long term condition
MZ	Monozygotic
NHS	National health service
NICE	National institute of clinical excellence
NIHR	National institute of health research

PACC	Perigenual anterior cingulate cortex
PFC	Prefrontal cortex
PIT	Psychodynamic interpersonal therapy
PNS	Parasympathetic nervous system
PV	Plasma viscosity
QA	Quality assessment
QoL	Quality of life
RCT	Randomised controlled trial
RMSEA	Root mean square error approximation
SAM	Sympathetic adrenal medullary
SB	Safety behaviour
SD	Standard deviation
SEM	Structural equation modelling
SNS	Sympathetic nervous system
SSRI	Selective serotonin reuptake inhibitor
TAU	Treatment as usual
TCA	Tricyclic antidepressant
TCBT	Therapist cognitive behavioral therapy
TLI	Tucker-lewis index
TTGA	Tissue transglutimaise
VSI	Visceral sensitivity index
WL	Wait list
WSA	Work and social adjustment
WSAS	Work and social adjustment scale
X^2 GOF	Chi square goodness of fit

1. Introduction to Irritable Bowel Syndrome

1.1 Definition of IBS

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder (FGID) characterised by both bowel and abdominal symptoms. It falls under the umbrella term of "medically unexplained symptoms/long term conditions" (MUS/LTC), which are characterised collectively as syndromes consisting of persistent physical symptoms with no clear physiological cause (Deary, Chalder, & Sharpe, 2007). Diagnostic criteria have been developed to provide definitive criteria for IBS. The Manning Criteria is a diagnostic criteria that has largely been superseded by the development of the Rome criteria (Drossman, 2016). The Manning Criteria identified six key symptoms that identified a diagnosis of IBS as distinct from other potential FGIDs. These included (i) visible abdominal distension (ii) pain relieved by a bowel action (iii) more frequent stools with the onset of pain (iv) looser stools with the onset of pain (v) rectal passage of mucus (vi) sensation of incomplete evacuation (Talley et al., 1990). The more symptoms present in an individual, the higher the likelihood of IBS. However the criteria did not suggest a threshold number of symptoms necessary for diagnosis and therefore diagnoses of IBS have been made with as little as two of the six symptoms present across research studies (Saito et al., 2000).

A more rigorous criterion for diagnosis in IBS called the "Rome criteria" was developed by a working group of clinical experts (Saito et al., 2000). Such criteria have been subsequently refined in numerous iterations based on continuing research and expert observations (Drossman et al., 2011). The most recent set of criteria is the Rome IV (Drossman, 2016). These stipulate that the experience of abdominal symptoms such as pain and/or bloating must be associated with altered bowel movements or stool consistency. These symptoms have to have been experienced a minimum of once a week consistently for at least six months, to constitute a diagnosis of IBS. There are three notable changes in the definition and characterisation of IBS in Rome IV compared to Rome III (Drossman, 2016). The first change relates to the removal of the term 'discomfort' in application to abdominal pain. The Rome III stipulated that individuals must experience "abdominal pain or discomfort". It was presumed that these terms described a continuum of abdominal pain severity, with 'discomfort' describing less severe pain. It has been shown however, that individuals interpret pain and discomfort as qualitatively different constructs, with discomfort potentially incorporating a range of symptoms (Shah, Bhatia, & Mistry, 2001). The Rome IV has therefore reduced

ambiguity, by using the term “pain” only, to describe the question regarding abdominal pain severity.

The Rome III classification identified four IBS subtypes according to the proportion of stools that were hard/lumpy compared to those that were loose/watery (table 1.1). The four subtypes are constipation predominant IBS (IBS-C) (loose/watery stools <25%, hard/lumpy stools >25%), diarrhoea predominant IBS (IBS-D) (loose/watery stools >25%, hard/lumpy stools <25%), alternating/mixed pattern IBS (IBS-A) (loose/watery stools >25%, hard/lumpy stools >25%) and unclassified (IBS-U) (loose/watery stools <25%, hard/lumpy stools <25%). The Rome IV maintains these classifications of bowel pattern subtypes, however makes the important distinction that classifications are based on the proportion of symptomatic stools rather than all stools (i.e. stools when a-symptomatic).

The next change to the criteria was with specific regard to the relationship between IBS and other functional bowel disorders. Instead of identifying IBS, with its composite bowel pattern subtypes as distinct disorders, the Rome IV considers IBS to exist on a spectrum of symptom presentations. This change acknowledges that there are linked pathophysiological features of differing functional bowel disorders and that symptoms may overlap between different diagnostic criteria. The Rome IV explicitly states therefore that patients may transition across diagnoses or have combinations of diagnoses that could require overarching treatment approaches.

A key limitation of the Rome criteria across all of the iterations is that it is not generally adopted in clinical practice to diagnose IBS (Moayyedi et al., 2017; Chang et al., 2018). A recent study found that only about a third of GPs in primary care across European countries regularly used the criteria for diagnosis of IBS (Mujagic et al., 2017). The result of this is often that patients with IBS receive a diagnosis by exclusion. This is described and discussed further in section 1.8.

Table 1.1: ROME III classifications of IBS bowel subtypes

	Stool Type	
Bowel Subtype	Loose/Watery	Hard/Lumpy
IBS-D	>25%	<25%
IBS-C	<25%	>25%
IBS-A	>25%	>25%
IBS-U	<25%	<25%

1.2 Physiology of the Digestive Process and IBS

1.2.1 Normal gut digestion and motility

Figure 1.1 depicts the gastrointestinal (GI) tract, which includes the key areas involved in digestion and GI motility. At the top of the figure is the oesophagus, which transports food from the mouth to the stomach. After each swallow, peristaltic (synchronised) contractions allow the sphincter between the oesophagus and the stomach to open, enabling the food to travel from one to the other. Once in the stomach, the food is ground down and mixed with digestive juices to allow later absorption when it reaches the small intestine. To achieve this, there are rhythmic synchronized contractions in the lower part of the stomach, which push waves of food and digestive juices against a closed pyloric sphincter muscle. The stomach then empties by moving the food into the small intestine at a controlled rate facilitated by further slow contractions. Between meals, when the digestible content has left the stomach, further contractions occur, known as the migrating motor complex. These are occasional bursts of synchronised contractions that occur in conjunction with the opening of the pyloric sphincter muscle. They have the function of ridding the stomach of indigestible content. More, largely irregular, contractions occur in the small intestine, intended to move the food back and forth to mix it with digestive enzymes allowing absorption of the food. The contractions also move the contents of the small intestine to the large intestine (colon). It will usually take between 90 and 120 minutes to move the first portion of the meal that has been eaten, to reach the colon. The last portion of the meal may not reach the colon for five hours. Between meals the small intestine repeats a cycle of contractions every 90-120 minutes. This cycle consists of a period without contractions, a period of unsynchronised contractions similar to those that appear after eating and then a period of strong peristaltic contractions.

Discrete clustered peristaltic contractions may also occur at infrequent intervals in the upper small intestine. In addition to these, there are also giant migrating contractions, which are peristaltic over a long span of the intestine and may be part of a reflex that sweeps bacteria and food debris out of the intestine. In healthy people neither of these contractions cause substantial sensation or pain (Johnson et al., 2012). Contractions in the colon can be subdivided into non-peristaltic contractions, designed to move the contents of the colon back and forth to allow ultimate reabsorption of liquids, and high amplitude propagating contractions (HAPC), intended to move the contents forward. It

is these contractions that begin at the top of the colon and sweep round, down to the rectum producing a stool or urge to pass a stool.

The enteric nervous system (ENS) is part of the autonomic nervous system (ANS). It is made up of 500 million neurons and located in the walls of the gastrointestinal tract, reaching from the oesophagus to the anus (Fichna & Storr, 2012). Although the general structure of the ENS is similar whether it is located in the oesophagus or the colon, it is not necessarily the case that it operates similarly in the different parts of the GI tract (Furness, 2008). The role of the ENS in IBS is presented in further detail below (1.4.1), however generally in healthy gut function the ENS is the mechanism by which contractions and gut function are coordinated with the central nervous system (CNS). "Efferent pathways" refer to the signalling channel from the CNS (brain) to the ENS (gut), whilst "afferent pathways" are the channels in reverse from the gut to the brain.

1.2.2 Digestion and gut motility in IBS

Gut function has been observed to differ in IBS compared to normal functioning in healthy controls (Tanaka, Kanazawa, Fukudo, & Drossman, 2011). There are two main ways that gut function is different in those with IBS: altered motility and altered perceptions/ experiences of gut sensations (Mach, 2004; Tanaka et al., 2011). In IBS, motility can be observed to differ from that of healthy controls, as there appears to be a disruption in peristaltic contractions, which have become desynchronized (Garnett, 1999). Individuals with IBS-C have a decreased number of colonic contractions slowing gut transit, whereas individuals with IBS-D have a greater number of fast colonic contractions accelerating gut transit (Garnett, 1999; Mach, 2004). However, the exact patterns of motility responsible for IBS-D and IBS-C have not been established (Drossman, Camilleri, Mayer, & Whitehead, 2002).

Abnormal contractions in the GI tract can also account, at least in part, for the abdominal pain experienced in IBS (Kellow & Phillips, 1987; Chey, Jin, Lee, Sun, & Lee, 2001; Drossman et al., 2002). Individuals with IBS who experience abdominal pain and diarrhoea have been shown to have significantly more clustered peristaltic contractions in the small intestine, which are of higher amplitude than those observed in healthy controls (Drossman et al., 2002). These types of contractions are thought to be associated with abdominal pain (Drossman et al., 2002) however there is little empirical evidence to support this assertion (Delvaux, 2002). The motility abnormalities may interact with low sensory thresholds to produce IBS symptoms. For example, the delayed transit of gas has been shown to increase abdominal perception in IBS (Serra,

Azpiroz, & Malagelada, 2001). Furthermore those with IBS perceive the occurrence of normal migrating motor complex significantly more than controls (Kellow, Eckersley, & Jones, 1991). An area of research in IBS, which is fast growing relates to the apparent visceral hypersensitivity within the bowels in IBS (Delvaux, 2002; Poitras, Poitras, Plourde, Boivin, & Verrier, 2002). Visceral hypersensitivity refers to the tendency to experience pain within the inner organs – in IBS, the GI tract – at a more intense level than the average individual (Delvaux, 2002; Drossman et al., 2002). Research has shown that individuals with IBS have enhanced visceral perception in various regions of the GI tract including the oesophagus, stomach and small intestine (Delvaux, 2002; Drossman et al., 2002). The potential mechanics and pathophysiology of visceral hypersensitivity is further described in the sections below.

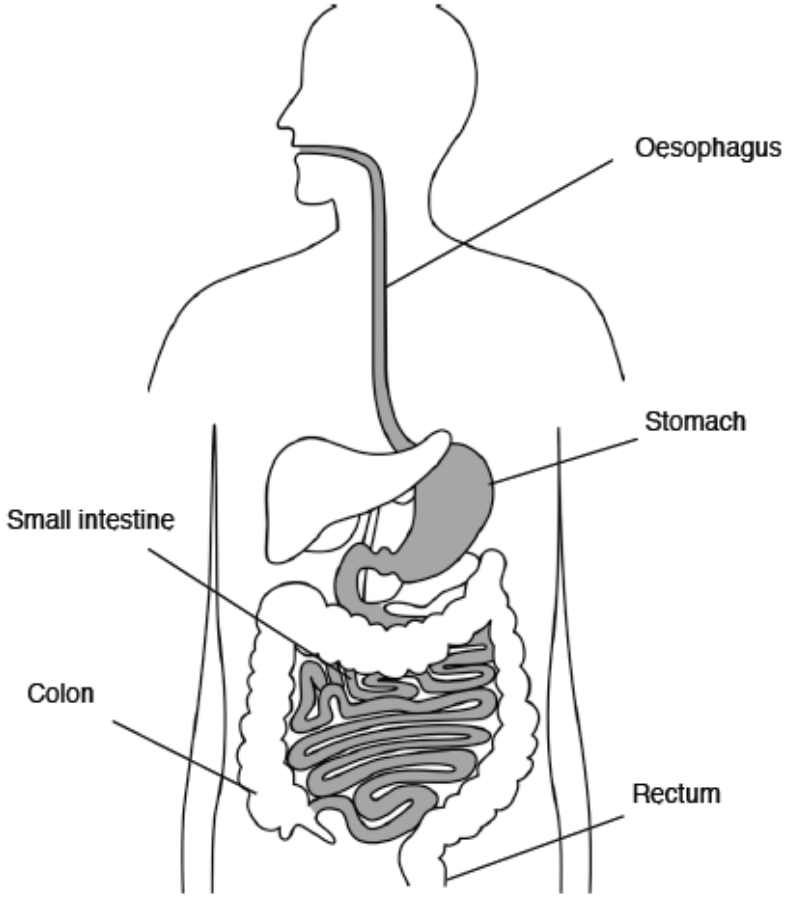

Figure 1.1: Anatomy of the gastrointestinal tract involved in digestion and motility

1.3 Prevalence of IBS

IBS is a particularly prevalent syndrome, estimated to affect between 10 and 22% of the UK population (Hellier, Sanderson, Morris, Elias, & De Caestecker, 2006) with a similar prevalence in the US (Hungin et al., 2008) and Europe (Quigley, Bytzer, Jones, & Mearin, 2006). Previously research has indicated that IBS has a higher prevalence in Western countries as opposed to non-Western countries (Husain et al., 2008). However, more recently it appears that the prevalence is increasing amongst these countries as individuals adopt a more 'Western lifestyle' (Gwee, 2005; Kang, 2005). This could suggest that cultural or dietary factors impact on the incidence of IBS. The role of social influences are considered in section 1.6.1. Variation in reported prevalence rates may also be in part due to the use of different diagnostic criteria (Hungin, Whorwell, Tack, & Mearin, 2003). In addition to the present and previous iterations of the Rome criteria, some studies utilise the Manning Criteria or rely on the use of self-identified IBS (Lovell & Ford, 2012b) and therefore estimations of prevalence can contrast quite substantially. A meta analyses of prevalence studies found that studies utilising the Manning Criteria had higher calculations of prevalence (Lovell & Ford, 2012b). This equated to a 14% prevalence rate as compared to 8.8% (Rome I) and 9.4% (Rome II). The study was conducted prior to the development of the Rome III or IV.

1.3.1 Bowel pattern subtypes

Studies assessing the prevalence using iterations of the Rome criteria have also varied in terms of the estimation of the prevalence of the specific bowel pattern subtypes. Until the Rome III criteria, IBS-A and IBS-U were not explicitly defined (Dorn et al., 2009), which may be another factor affecting estimates of subtype prevalence. However, a comparison of subtype prevalence across Rome I and II criteria found high agreement in terms of subtype classifications and stability (Dorn et al., 2009). Since the development of the Rome III criteria, research has generally demonstrated that IBS-A is the most prevalent subtype with IBS-U being the least common subtype (Guilera, Balboa, & Mearin, 2005; Longstreth et al., 2006; Su, Shih, Presson, & Chang, 2014). This is however highly variable across studies, with some finding that IBS-A is the least prevalent subtype (Engsbro, Simren, & Bytzer, 2012). The variability in IBS subtype distribution is said to be affected by geographical location, the particular population being sampled (e.g. female only, particular age, etc.) and the criteria employed to classify subtypes (Guilera et al., 2005). The validity of the bowel subtypes as identified by the Rome criteria has also been questioned. This is due to an inconsistency between

subtypes identified according to the Rome criteria and self-reported experience of subtypes (Hungin et al., 2003). For example, the rate of IBS-A was found to be much higher using Rome II (63%) when compared to self-report (21%) (Hungin et al., 2003). This perhaps questions the utility of the Rome criteria in classifications of bowel pattern subtypes. There may also be inconsistency in bowel pattern subtypes within individuals as studies have demonstrated that individuals can transition across the different bowel pattern subtypes (Mearin et al., 2004; Guilera et al., 2005). It has been predicted that the Rome IV criteria may further change the distributions of the classifications, potentially reducing the amount of individuals identifying as IBS-U (Drossman, 2016).

1.3.2 Female predominance

There appears to be consistency across studies utilising different diagnostic criteria, in identifying a female predominance in IBS (Kang, 2005; Lovell & Ford, 2012a, 2012b). A gender difference in prevalence across the IBS subtypes has also been shown in a meta-analysis assessing gender differences in IBS (Lovell & Ford, 2012a). IBS-C was more common in women and IBS-D was more common in men (Lovell & Ford, 2012a), while IBS-A was generally equally distributed across genders. The pooled prevalence of IBS-C was 40% for women, compared to 21% in men. In contrast the prevalence of IBS-D in women was 31% compared to 50% in men. Whilst some studies have indicated that geography does not affect the female predominance in IBS (Kang, 2005), other research has suggested that prevalence of IBS in women was not significantly higher in studies conducted in South Asia, South America or Africa (Lovell & Ford, 2012a). Nevertheless, the authors concluded that a modestly higher prevalence in women than men is generally stable according to geography.

1.3.3 Age

In addition to gender, age is another factor found to affect the prevalence of IBS. In most studies the IBS prevalence rate declines with age (Kang, 2005). The odds of IBS in those aged 50 years or older was significantly lower than in those younger than 50 years (OR, 0.75; 95% CI, 0.62-0.92) (Lovell & Ford, 2012b). Although IBS has been found to occur in all age groups including children, adolescents and the elderly, it has been found that 50% of individuals with IBS report first experiencing symptoms before the age of 35 years old (Canavan, West, & Card, 2014).

1.3.4 Socioeconomic status

Unlike age, there is limited research reporting the prevalence of IBS according to socioeconomic status. In the 2012 meta-analysis, pooled data from the only four studies reporting on socioeconomic status in IBS, suggested that there was no significant difference in prevalence in high compared to low socioeconomic groups (Lovell & Ford, 2012b). Since the review, however, there have been further studies reporting on this with contradictory findings (Canavan et al., 2014). While one study suggested IBS was associated with low socioeconomic status, two other studies suggested the opposite, showing a higher prevalence of IBS amongst those who have a higher socioeconomic group during childhood (Canavan et al., 2014). Although the evidence is limited, the authors postulate that the results could indicate that greater internalisation of stress that comes with a particular kind of work and role in higher earning groups, has a role in the onset and/or maintenance of IBS symptoms. Identifying groups and areas in which IBS is more or less prevalent is important for building an understanding of aetiology in IBS.

1.4 Biopsychosocial Aetiological Understanding of IBS

The aetiology of IBS is largely accepted to be of biopsychosocial origin (Drossman, 2016). This conceptualises the pathogenesis and clinical experience of IBS as an interacting mixture of biological, psychological and social factors. Figure 1.2 depicts the biopsychosocial model of IBS. It illustrates how individuals may have a number of factors predisposing them to developing IBS. These factors may be biological (genetics), psychological (personality factors, trauma) or social (culture and environment). Predisposing factors interact with precipitating factors, which may also be biological, psychological or social, in nature (figure 1.2). For example a bout of gastroenteritis may trigger the initial onset of IBS in an individual who has grown up in an environment that regards bowel symptoms as shameful or overly focuses on bowel movements. IBS symptoms are then perpetuated by a cycle of biopsychosocial factors, such as increased sensitivity, altered immune function, unhelpful cognitions regarding symptoms, anxiety, unhelpful behavioural responses and perceived social support.

The framework of understanding IBS has been important in establishing interdisciplinary treatment approaches for IBS (Drossman, 2016). The model demonstrates how there can be substantial variability of the different factors involved in onset and maintenance of IBS across individuals. This is better understood through consideration of the separate spheres of aetiology: biological, psychological and social, which are considered in more detail below. A physiological system by which interaction

of these three spheres may occur is referred to as the “brain-gut axis” (BGA) (Jones, Dilley, Drossman, & Crowell, 2006).

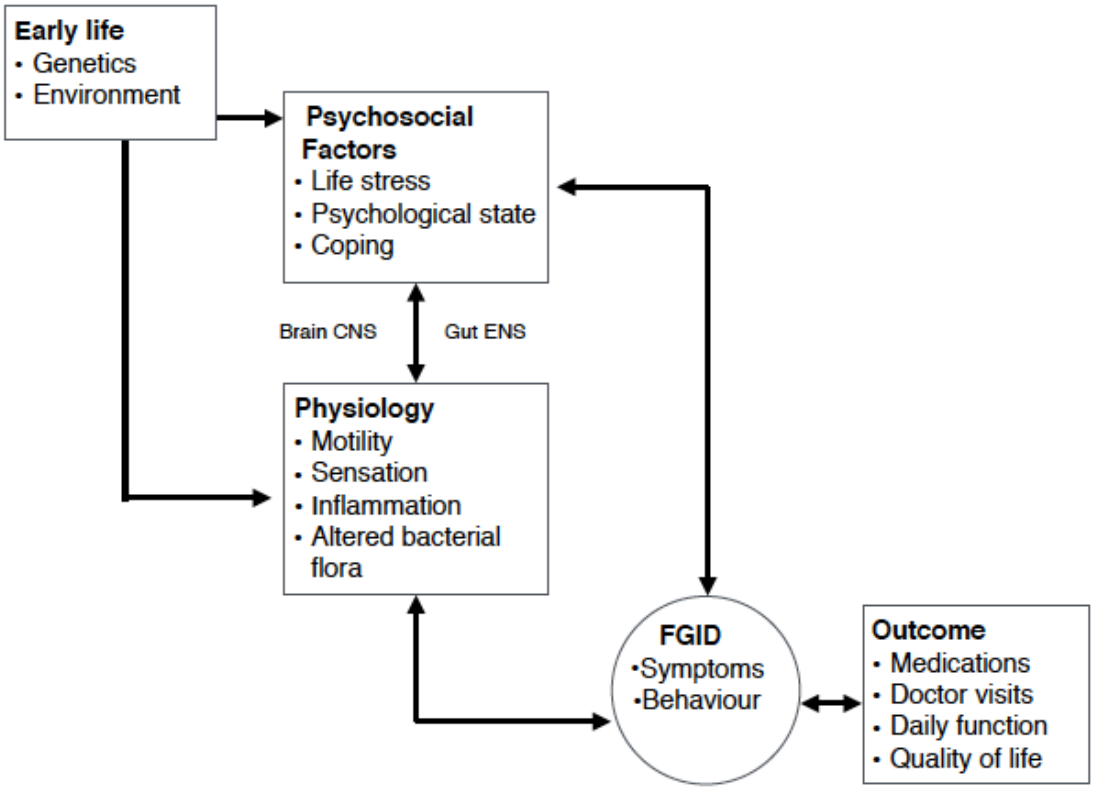

Figure 1.2: Biopsychosocial Model of IBS (Halpert & Drossman, 2005)

1.4.1 Brain-gut axis

The Brain-Gut Axis (BGA) is a term used to refer to the bidirectional communication network between the central nervous system (CNS) and the enteric nervous system (ENS). The CNS comprises the brain and spinal chord, and neuronal signalling allows communication between structures within the network. The CNS coordinates and controls most functions of the body and the mind. The ENS has been called the ‘second brain’ as it has the ability to act autonomously from the other arms of the nervous system (Furness, 2008). It is also able to integrate information in the same way as the brain does, without CNS input, due to the fact that it includes efferent neurons, afferent neurons and interneurons (Mayer, 2011). Efferent neurons carry information from the CNS to organs and muscles throughout the body, while afferent neurons carry

information from organs and muscles to the CNS. Interneurons transmit impulses between neurons allowing decisions on whether incoming signals warrant response (Mulak & Bonaz, 2004). As such the ENS can receive and send information to the CNS as well as integrating different information and adapting signalling accordingly.

The two key brain regions of importance in the CNS with regards to IBS, are the limbic system and the prefrontal cortex (PFC) (Jones, Dilley, Drossman, & Crowell, 2006). The limbic system is also referred to as the 'emotional motor system', 'emotional brain' and, prior to that, the 'visceral brain' due to its role in emotion formation and regulation (Mach, 2004). The limbic system is anatomically comprised of the amygdala, hypothalamus, medial thalamus and anterior cingulate cortex (Jones et al., 2006). The amygdala is heavily involved in emotional processing including the formation of emotionally conditioned responses (e.g. fearful avoidance), the consolidation of emotional memories and the processing of social signalling of emotions (e.g. facial expressions or posture) (LeDoux, 2000; Dalgleish, 2004). Together with the amygdala the thalamus processes information about incoming sensory signals to determine perception of threat (Jones et al., 2006).

The hypothalamus provides a link between the CNS and the ANS, which is the part of the nervous system that orchestrates the automatic stress response. In addition to the ENS, there are two other branches of the ANS. These are the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS prepares the body for intense physical activity as in the 'fight or flight' stress response, while the PNS regulates general autonomic functioning (e.g. digestion, defecation, urination and heart rate) to keep the body operational. The PNS is responsible for inhibiting high-energy processes triggered by the SNS. During the stress response, the SNS is activated by the amygdala registering a threat and sending signals to the hypothalamus. It is the hypothalamus that allows communication with the rest of the body as it fires neurons to activate the adrenal glands. The adrenal glands respond by releasing the hormone epinephrine (also known as adrenaline) into the blood stream. This causes a number of physiological changes, such as increased heart rate and blood pressure, increasing blood flow to particular organs and muscles including the bowels. Epinephrine also triggers the release of blood sugar and fats from temporary storage into the blood stream allowing increased energy to all parts of the body. This initial 'fight or flight' process in response to stress is known as the sympathetic adrenal medullary (SAM) system. The initial stress response can therefore have a direct effect on gastric motility, which can be disrupted in the process of altered autonomic processes.

The second component of the stress response system is also activated by the hypothalamus. This is known as the Hypothalamic-Pituitary-Adrenal (HPA) axis, and is activated as the initial surge of epinephrine subsides. If the amygdala continues to register a threat after the initial response, the hypothalamus will release corticotropin-releasing hormone (CRH), which travels to the pituitary gland and triggers the release of adrenocorticotropic hormone (ACTH). In turn this travels to the adrenal glands and prompts the release of the stress hormone cortisol. This has the effect of keeping the body on high alert and vigilant to potential perceived threats. Together, the amygdala and the hypothalamus therefore have a key role in threat perception and stress response activation.

The anterior cingulate cortex (ACC) is the other key brain area within the limbic system that has been implicated as an important component of the BGA in IBS (Morgan, Pickens, Gautam, Kessler, & Mertz, 2005; Jones et al., 2006; Hall et al., 2010; Tillisch & Labus, 2011; Kennedy et al., 2012). The ACC is said to have a 'cognitive' dorsal subdivision and an 'affective' ventral subdivision, which is also called the perigenual ACC (pACC) (Jones et al., 2006). Increasingly research suggests that the ACC monitors the functional state of the body and detects any new information that may cause conflict and give rise to affective or emotional consequences (Bush, Luu, & Posner, 2000; Dalgleish, 2004). It therefore integrates visceral, attentional and affective information, and when potential conflicts are detected, the ACC signals to the PFC (Jones et al., 2006).

The PFC has a wide variety of functions and is often termed the 'executive control centre'. This is because it is responsible for integrating together multiple sources of informational input from different areas of the brain. It uses the integrated information as a basis for decision-making processes and planning (Jones et al., 2006). In the context of the BGA, the PFC's role is to form integrated multisensory representations about gut function homeostasis, food intake and visceral pain (Mayer, 2011). The BGA therefore is an important network to maintain the healthy regulation of food intake, digestion, motility and gut sensations (Fichna & Storr, 2012).

Disruptions within the BGA at any level, whether structural or functional can therefore result in FGIDs such as IBS (Mach, 2004; Jones et al., 2006; Mayer, 2011; Fichna & Storr, 2012; Kennedy et al., 2012). In IBS both gut motility and abdominal pain/hypersensitivity may be due to dysfunction in the BGA. Researchers have suggested that disruption in the BGA may be the result of alterations in the ENS (bottom up model) or the result of alterations affecting the CNS (top down model) (Mulak &

Bonaz, 2004). It is also possible that IBS symptoms are produced by a combination of both. The ENS, when functioning correctly, is programmed to provide local reflexes such as the migrating motor complex and the peristaltic reflex (section 1.2, physiology of IBS). A disruptive stimulus in the gut such as an infectious event, or the presence of food or bile acids, can therefore trigger an alarm signal to the CNS (Mach, 2004; Mulak & Bonaz, 2004). This would be an instance of bottom up BGA disruption. As such physiological factors can have a causative role in IBS. These are considered further below. Top down processing involves the CNS transmitting inhibitory efferent signals to inhibit the afferent pain signals (i.e. pain signals coming from the gut). The CNS's prioritization of the amplification or diminishment of pain signals is dependent on relevant environmental and internal perceptions (Jones et al., 2006). As such it is likely that the bidirectionality of transmissions along the BGA allow both the CNS and ENS to work in tandem in order to determine both pain sensations and motility in IBS (Mayer, 2011; Mayer & Tillisch, 2011; Tillisch & Labus, 2011; Fichna & Storr, 2012). Furthermore, as the limbic system is implicated in the integration of emotional, visceral and attentional information, cognitive, behavioural and emotional factors are likely to impact on the dispersal of inhibitory efferent pain signals determined by these brain regions (Jones et al., 2006).

1.5 Biological/Physiological Aetiological Factors

1.5.1 Visceral hypersensitivity

Visceral hypersensitivity has been identified as a characteristic amongst individuals with IBS, and one that may be involved in the pathogenesis of abdominal pain that is experienced in IBS. To date the exact cause of visceral hypersensitivity in IBS is unknown (Delvaux, 2002). A method of assessing pain thresholds in the bowels is called 'barostat distension' in which a balloon is inserted into the colon and slowly inflated to different pressure levels. The exercise is known to cause abdominal pain, which is thought to be the result of the direct impact of the balloon on the internal walls of the colon. One seminal study introduced this technique in the context of IBS, finding that individuals with IBS reported pain when the balloon was at a lower volume than healthy controls (Ritchie, 1973). This study has since been replicated in a number of studies that corroborate these findings showing that in 50-70% of IBS patients the threshold for reporting pain is below that of healthy controls (Drossman et al., 2002).

This observable sensitisation may be caused by peripheral mechanisms localised to the bowels involving afferent signalling from the ENS to the CNS (Halpert & Drossman,

2005; Azpiroz et al., 2007). It may also be the result of central sensitisation in the CNS whereby signalling between the brain and the gut becomes hyperactive and abdominal activity and sensation is inappropriately exaggerated (Halpert & Drossman, 2005; Azpiroz et al., 2007). Support for peripheral sensitisation as opposed to central sensitisation comes from the fact that visceral pain hypersensitivity is generally limited to sensitivity in the viscera (i.e. the organs) and not extended to the somatic system (i.e. tissue pain) in IBS (Cook, van Eeden, & Collins, 1987; Accarino, Azpiroz, & Malagelada, 1995). This may suggest that the mechanism is localised rather than centralised (Azpiroz et al., 2007). Furthermore IBS is known to occur after irritation of the gut by infectious agents (Gwee et al., 1999; Mearin et al., 2005). Establishing that exaggerated signals from the gut cause the visceral sensitivity demonstrated in IBS, is difficult due to the fact that there are no valid instruments able to assess the signal at the level of the gut or spinal chord (Azpiroz et al., 2007).

The alternative hypothesis that disruption in particular brain circuits involving the limbic system and prefrontal cortex are involved in the central modulation of visceral hypersensitivity in IBS, is informed by the field of somatic pain research (Verne & Price, 2002; Azpiroz et al., 2007; Zhou & Verne, 2011). There appear to be two main neural networks that have been shown to function abnormally in brain imaging studies of visceral pain in IBS (Kennedy et al., 2012). These include the emotional-arousal network, which is heavily implicated in the BGA and the lateral prefrontal regions of the descending pain inhibitory network (limbic system and PFC, amongst other regions beyond the scope of this thesis), which also interact with the BGA (Tillisch & Labus, 2011). Both of these networks are impacted by and involved in affective responses such as threat processing, fear (Halpert & Drossman, 2005; Azpiroz et al., 2007; Tillisch & Labus, 2011; Kennedy et al., 2012) and cognitions, such as anticipatory processes, attentional control and reappraisal (Tillisch & Labus, 2011; Kennedy et al., 2012). Psychosocial factors are therefore pertinent to the development of visceral hypersensitivity.

There is also the likely possibility that both peripheral and central sensitisation can have a role in the pathophysiology of IBS, rather than the two hypotheses being mutually exclusive. It is important to acknowledge that visceral hypersensitivity is but one aspect of IBS and not one that is universal to everyone who has IBS (Azpiroz et al., 2007; Zhou & Verne, 2011). Furthermore, the experience of visceral hypersensitivity itself, within IBS, is also heterogeneous. While for some individuals it is localised to a particular part of the GI tract, for others it may be distributed across the entire GI area. Consequently,

the extent to which understanding the pathophysiology of visceral sensitivity can inform our aetiological understanding of IBS is limited. What the evidence for both peripheral and central sensitisation shows, is that both physical (e.g. infectious event) and psychological factors (e.g. affective arousal) can trigger such sensitisation (Halpert & Drossman, 2005; Azpiroz et al., 2007; Tillisch & Labus, 2011; Kennedy et al., 2012)

1.5.2 Gut microbiota

In the last ten years there has been an increase of research into the role of gut microbiota, with particular focus on its potential aetiological role in IBS (Cryan & Dinan, 2012). Gut microbiota is the term given to a dense microbial ecosystem consisting of bacterial cells. In healthy individuals there is estimated to be around 195 bacterial strains (Collins, 2014). Healthy gut microbiota are characterised by diversity in strains and stability in the balance across them. "Dysbiosis" refers to the loss of microbial diversity and temporal instability, which is advocated as a potential cause of bowel dysfunction (Collins, 2014; Ringel & Ringel-Kulka, 2015). However it is acknowledged in a recent review of the role of microbiota in IBS, that dysbiosis is unlikely to account for all instances of IBS (Collins, 2014). This is because not all individuals with IBS have abnormal bacterial counts compared to healthy controls (Posserud, Stotzer, Björnsson, Abrahamsson, & Simrén, 2007; Öhman & Simrén, 2010).

Evidence that gut microbiota may have a role in the expression of IBS primarily comes from animal studies. These have demonstrated that antibiotic-induced dysbiosis resulted in changes to gut motility (Collins & Bercik, 2009; Anitha, Vijay–Kumar, Sitaraman, Gewirtz, & Srinivasan, 2012; Chassard et al., 2012) as well as increases in visceral pain responses in barostat distension (Verne & Price, 2002; Verdu et al., 2006). Microbiota have been shown to exert effects on gut motility and sensitivity at different levels within the BGA with bidirectional effect (Moloney et al., 2016). This means that as well as impacting on gut physiology, the microbiota can also affect mood and cognition (Cryan & Dinan, 2012; Collins, 2014; Moloney et al., 2016). Rat and mice studies compare germ-free rodents with abnormally low levels of gut microbiota to control counterparts with normal gut microbiota levels. Such studies have found that germ-free mice have an exaggerated release of ACTH (stress hormone) when exposed to mild stress (Cryan & Dinan, 2012), display changes in emotive behaviour (Cryan & Sweeney, 2011; Collins, 2014) and display deficits in non-spatial and working memory tasks (Gareau et al., 2010). As such microbiota may not only contribute to changes in gut functioning and sensations but also contribute to changes in anxiety, cognitions and behaviour (Collins, 2014). Importantly, there are multiple physiological and psychological factors that affect

gut microbiota levels. These include psychological stress, diet and the administration of antibiotics (Cryan & Dinan, 2012; Collins, 2014; Distrutti, Monaldi, Ricci, & Fiorucci, 2016; Moloney et al., 2016).

1.5.3 Genetics

It has been suggested that there is a hereditary component to IBS. Studies have found that there is a concordance rate of 17.3% in monozygotic (identical) twins and 8.4% in dizygotic twins (Levy et al., 2001). Whist this would support the assertion that there may be a predisposing genetic role in IBS, it would also suggest that there are other factors involved. This is because the concordance rate is not 100% or even close, demonstrating a variability in the onset of IBS that is unaccounted for. The literature examining the extent of genetics in the aetiology of IBS, generally accepts that whilst there may be a contribution of genes to the development of IBS, complex biopsychosocial interactions are also involved (Saito, 2011)

1.6 Social Aetiological Factors

1.6.1 Social learning & environmental influences

The study by Levy et al compared the probability of having a mother with IBS with the probability of having a co-twin with IBS for monozygotic (MZ) twins with IBS (Levy et al., 2001). Monozygotic twins have 100% the same genetics, whereas mothers share approximately 50% of genes with their children. Therefore, from a genetic point of view the probability that the mother of an MZ twin has IBS should be lower than the probability that the MZ co-twin has IBS. However, the findings indicated that having a mother with IBS accounted for as much variance as having an identical set of genes with an MZ co-twin who has IBS. This would indicate that the contribution of social learning to IBS is at least as great as the contribution of heredity. Social learning in this context includes both the likelihood for children to observe and display parental behaviours (modelling) and the conditioning of behaviours by parental reinforcement. There is evidence for both types of learning in IBS (Van Oudenhove et al., 2016).

Evidence for modelling comes from studies showing a strong association between parental anxiety and somatization and children's abdominal symptoms (Walker, Garber, & Greene, 1991; Campo et al., 2007; Seino et al., 2012). Research in the wider context of functional illness and somatic complaints examining the social learning hypothesis that illness behaviour can be learned, lends support to the notion that this can occur in IBS (Scharff, 1997). An example of social learning IBS illness behaviours would be if a

child observed their mother or father's tendency to pay close attention to their abdominal sensations. The child would learn that monitoring such sensations is important and the consequent behaviour (such as going to the toilet for long periods) may also be learned.

The basic principle of positive reinforcement is the rewarding of a behaviour that increases the likelihood of the same behaviour to occur again. Behavioural reinforcement in IBS may occur where a child expresses worry about a particular symptom and the parent/s may reward this with increased attention, sympathy or indulgence. In an experimental study, parents were asked to either show positive and sympathetic responses to their children's pain or to ignore it (Walker et al., 2006). The frequency of pain complaints were higher in the positive/sympathetic group than the group instructed to ignore the children. This demonstrated that when the complaining behaviour was rewarded, it was reproduced. Outside of experimental settings, it has also been shown that children whose mothers reinforce illness behaviour, experience more severe stomach aches and more school absences than other children (Levy et al., 2001).

1.6.2 Early adverse life events

Early adverse life events are traumatic experiences during childhood that encompass physical, emotional or sexual abuse as well as conflicting relationships with the primary care giver or loss of a parent (Bradford et al., 2012). In comparison to controls, individuals with IBS have a significantly higher reported prevalence of early adverse life events than healthy controls (Bradford et al, 2012). In particular the instances of physical, emotional and sexual abuse are much higher than reported in healthy control groups (Bradford et al, 2012). Other studies have similarly demonstrated that there is a high prevalence of sexual abuse history within the IBS population (Drossman, Talley, Leserman, Olden, & Barreiro, 1995; Ross, 2005). The mechanism by which such events may have a role in the onset of IBS is likely to involve the BGA and stress response systems (Halpert & Drossman, 2005). The onset of IBS is likely associated with the increased psychological stress that occurs in the face of these traumatic events (Van Oudenhove et al., 2016)

1.7 Psychological Aetiological Factors

1.7.1 Stress and psychological distress

Psychological stress is commonly identified within the literature (Drossman et al., 2002; Drossman, 2016) and by patients (Håkanson, 2014) as a probable trigger of IBS.

Psychological stress occurs when an individual perceives that environmental demands exceed their capacity to cope with them (Cohen, Janicki-Deverts, & Miller, 2007). Psychological stress and psychological distress are rarely teased apart conceptually, as they are highly interconnected (Ridner, 2004). Psychological distress can be understood as the emotional reaction that accompanies the experience of perceived stress (Cohen, Kamarck, & Mermelstein, 1994). For the purposes of discussing the aetiological role of stress in IBS, the term "stress" will be used to refer to the experience of psychological stress that is psychologically distressing. The hypothesis is that both intense periods of acute stress and chronic levels of stress can cause abnormal functioning in the bowel because of the close connection between the brain and the gut (Tanaka et al., 2011; Lovell & Ford, 2012b; Drossman, 2016; Van Oudenhove et al., 2016). While the effects of stress on gut function is not specific to those with IBS and are observable in healthy controls (Murray et al., 2004), research suggests that individuals with IBS may have a greater reactivity to stress (Drossman, 2005; Chang, 2011). This has been investigated using brain-imaging studies (Drossman, 2005), measures of CNS functioning (Fukudo & Suzuki, 1987; Patacchioli, Angelucci, Dell'Erba, Monnazzi, & Leri, 2001; Berman et al., 2002; Posserud et al., 2004) such as the comparison of salivary cortisol of IBS patients compared with healthy controls (Patacchioli et al., 2001) and psychological self report measures (Whitehead, Crowell, Robinson, Heller, & Schuster, 1992). Furthermore stress has been associated with the onset of IBS symptoms (Drossman et al., 2002; Chang, 2011) with high levels of perceived stress identified as a risk factor for those with gastroenteritis to develop IBS (Spence & Moss-Morris, 2007).

1.7.2 Precipitating affective disorders

While it is established that there is a high co-morbidity of anxiety and depression in IBS (presented in section 1.10.2), it has also been postulated that these affective disorders may have a predictive role. Along with high levels of perceived stress, anxiety was also found to be a significant risk factor for developing IBS after a bout of acute gastroenteritis (Spence & Moss-Morris, 2007). A recent meta-analysis combined the results of studies assessing anxiety and depression as risk factors for the onset of IBS and found that self-reported anxiety and depression provided a twofold risk for IBS onset (Sibelli et al., 2016). Both anxiety and depression appeared to play a stronger role in IBS onset for individuals with a gastrointestinal infection rather than individuals assessed in the general population. However, this difference could be attributed to differences in methodologies between these two types of study.

1.8 Diagnostic Procedures of Exclusion

The NICE guidance on the diagnosis of IBS recommends that individuals meeting the Rome criteria, also undergo some further tests to exclude other potential diagnoses such as inflammatory bowel disease or coeliac disease (Dalrymple & Bullock, 2008). These tests of exclusion are blood tests, which include a full blood count, c reactive protein (CRP), erythrocyte sedimentation rate (ESR) or plasma viscosity (PV) and antibody testing such as tissue transglutaminase (TTGA) or endomysial antibodies (Dalrymple & Bullock, 2008). A full blood count test is conducted to check for anaemia or other potential abnormalities that may account for symptom experience. CRP tests and ESR or PV tests are conducted to detect inflammation, which could be indicative of inflammatory bowel disease, while antibody testing such as TTGA is used to detect a potential diagnosis of coeliac disease. Should all of the blood tests be within the normal ranges, clinicians are advised to provide a diagnosis of IBS (Dalrymple & Bullock, 2008). It is however not uncommon for one of the tests to fall out of the normal ranges and require retesting (Spiegel, Farid, Esrailian, Talley, & Chang, 2010). If the individual is suffering with a virus, cold or other infection, they may have elevated CRP levels, for example. This would mean that individuals are required to have a retest to assess whether this was the cause of the elevation or whether further investigation is necessary.

Nice guidance also recommends that clinicians assess for 'red flag' symptoms that may be indicative of a serious organic disease (Dalrymple & Bullock, 2008). These red flag symptoms include unintentional and unexplained weight loss, rectal bleeding, a family history of bowel cancer or ovarian cancer or, for patients aged 60 or over, a sudden change in bowel habit to looser and/or more frequent stools that have persisted for more than 6 weeks. In addition to the suggested tests, individuals may opt to pay for further tests privately. Such tests may include ultrasonography, colonoscopy, thyroid function test, microscopy and culture for faecal ova and parasite or hydrogen breath tests for lactose intolerance and bacterial overgrowth. These tests are said not to be necessary for a diagnosis for IBS (Dalrymple & Bullock, 2008) however, patients frustrated with symptoms may pursue alternative methods of diagnosis and treatment (Bertram, Kurland, Lydick, Locke, & Yawn, 2001; Dhaliwal & Hunt, 2004; Quigley et al., 2006; Håkanson, 2014).

Actual patient experience of diagnosis is rarely as straight forward as the recommendations by NICE (Spiegel et al., 2010). Physicians may be anxious about providing a diagnosis that overlooks alternative diagnosis and consequently suggest

more tests, favouring a diagnosis of IBS by exclusion (Spiegel et al., 2010). It can therefore take a long time for individuals to receive a formal diagnosis of IBS, which can be upwards of 10 years in some cases (Meadows, Lackner, & Belic, 1997). In some cases individuals experiencing IBS may never receive a formal diagnosis from the doctor whereby they are definitively told that their symptoms are due to IBS (Hungin, Chang, Locke, Dennis, & Barghout, 2005). In these cases, individuals may have on their medical records a label of IBS, which may not have been adequately communicated to them (Owens, Nelson, & Talley, 1995; Chang et al., 2006).

One of the effects of having a diagnosis by exclusion is that individuals with an organic bowel disease such as inflammatory bowel disease (IBD) are unlikely to be diagnosed with IBS. There is both merit and disadvantages to this. Patients with IBD, who are not yet aware of their diagnosis are safeguarded by the process of diagnosis by exclusion. However, where patients are aware of their organic bowel conditions, it may be beneficial to receive an additional diagnosis of IBS. This would apply when the experience of particular symptoms such as persisting pain and urgency are not purely attributable to their primary diagnosis (Grover, Herfarth, & Drossman, 2009). Receiving an additional diagnosis of IBS may provide additional opportunity for symptom management outside of pharmacological treatments, utilising psychological techniques shown to be effective in IBS. In the long-term conditions literature, it is has been argued that the extent to which a symptom has an organic or 'non-organic' cause is irrelevant beyond the point of the likelihood of progressing physical damage (Grover et al., 2009). Persisting physical symptoms with known organic cause, can be managed in the same way as physical symptoms with unknown organic origins. Both involve the use of techniques to minimize the impact of such symptoms on everyday functioning and quality of life (Grover et al., 2009; Chacko, 2013; Coventry et al., 2015; Valovska, 2016).

1.8.1 The Necessity of a Diagnostic Criteria Specifically for IBS

Although it may be argued that IBS could be diagnosed using the Diagnostic and Statistical Manual 5 (DSM-5) under the criterion specified for 'Somatic Symptom Disorder', which no longer distinguishes between medically unexplained symptoms and organic disorder, (American Psychiatric Association, 2013; Regier, Kuhl, & Kupfer, 2013), . The diagnostic criteria for Somatic Symptom Disorder include:

A. One or more somatic symptoms that are distressing or result in a significant disruptions of daily life.

B. Excessive thoughts, feelings or behaviours related to the somatic symptoms
C. A persistent state of being symptomatic, even though the symptom may not be continuously present

While patients with IBS are likely to meet this criteria, there are important advantages to instead applying a more tailored criteria to diagnose IBS. A primary advantage being the perception of the syndrome by healthcare professionals. As the Rome criteria is biopsychosocially informed, it establishes a role for pharmacological treatment methods in IBS as well as psychological methods (Drossman., 2016). This is important because evidence suggests that the symptoms of IBS can be managed with medications such as antispasmodics or low dose antidepressants (Ford et al., 2009; Spiller et al., 2007). Should this guidance not be in place, it may limit effective treatment options for patients and increase the burden on already stretched resources for psychological treatments. The Rome criteria therefore makes primary care treatment more accessible for patients, which is important given the high prevalence of IBS symptoms.

An additional consideration is the stigma that may come with a diagnosis that is determined by a manual for 'mental disorders'. This may inhibit healthcare practitioners' tendencies to provide a diagnosis of 'somatic symptom disorder' in place of irritable bowel syndrome. Reluctance of healthcare providers to provide such a diagnosis can be seen elsewhere in the literature (Dimsdale et al., 2013; Rief & Martin, 2014). The consequence of this would be to create more uncertainty in patient prognosis and treatment journeys, which would likely impact on symptoms detrimentally.

A final issue with using the DSM-5 criteria in place of the Rome Criteria for IBS, is that such criteria are not sufficiently tailored to the symptoms and experience of IBS (Klemm et al., 2018). As such, the procedures for diagnosis do not guide clinicians to check for 'red flag' symptoms, to guard for risk of a more serious bowel disease.

1.9 Patient Experience

The result of potentially lengthy and perceivably unhelpful diagnostic procedures and healthcare consultations, is that individuals with IBS can often feel frustrated with healthcare services and professionals (Håkanson, 2014) as well as uncertain about their symptoms and health (Owens et al., 1995; Rønnevig, Vandvik, & Bergbom, 2009). It is not currently understood what distinguishes those that seek healthcare from those who do not. However one review postulated that psychosocial factors are important (Koloski, Talley, & Boyce, 2001). The authors suggested that healthcare seeking behaviour in IBS could be divided into three categories (1) non-consulters (2) sporadic consulters (3)

frequent consulters. Non-consulters were characterised as having greater coping abilities, but also potentially greater embarrassment and abnormal illness attitudes. Sporadic consulters were said to experience greater levels of distress and life events whilst those frequently consulting healthcare services had potential psychiatric co-morbidities, history of abuse and poor social support. The proposed model, although based on the results of a comprehensive review, has not been prospectively tested. Nevertheless, the importance of psychosocial factors in the context of healthcare professionals has been well advocated in the context of IBS (Drossman et al., 2002; Tanaka et al., 2011; Drossman, 2016). Integral to good clinician-patient interaction are five identified features: (1) empathy to patients' experience of illness (2) obtaining illness history and acknowledging the role of the patients' psychological factors (3) clarifying misunderstandings of the patient with regards to the illness (e.g. constipation is harmful) (4) educating the patient on self-management of the illness, including psychosocial factors (5) agreeing collaboratively a plan of treatment with the patient (Tanaka et al., 2011; Drossman, 2016).

Part of the problem encountered with healthcare professionals (HCPs) is the lack of knowledge possessed by general practitioners and nurses regarding the diagnostic criteria and symptoms of IBS (Longstreth & Burchette, 2003; Charapata & Mertz, 2006; Van Tilburg, Squires, Blois-Martin, Leiby, & Langseder, 2013). An integrated review of qualitative studies assessed the experience of IBS, including experiences with HCPS. Common themes emerging from a total of 144 participants were lack of information and support, unrecognised illness experiences and humiliating encounters (Håkanson, 2014). Humiliation appeared to primarily be the result of feeling that HCPs trivialised or dismissed symptoms being experienced. A key frustration and indeed apparent barrier to perceived ability to self-manage symptoms, was lack of clear diagnosis from physicians (Owens et al., 1995; Mira et al., 2015).

Uncertainty is an emergent theme in IBS qualitative studies. Unclear or confusing diagnoses are likely a key contributor to this and the lack of perceived control reported (Håkanson, 2014). Individuals with IBS report worrying not only about the experience of symptoms but about the potential threatening nature of them and the overarching effect that symptoms have on every day functioning (Rønnevig et al., 2009). The quality of life (QoL) of individuals with IBS is often much lower than healthy controls (El-Serag, Olden, & Bjorkman, 2002), and the everyday ability to engage in desired work and social activities is impeded (Casiday, Hungin, Cornford, de Wit, & Blell, 2008; Rønnevig et al., 2009; Farndale & Roberts, 2011). Patients cite having to sacrifice

elements of life to counteract the impact of symptoms as a cause of impaired functioning and QoL (Rønnevig et al., 2009). For example in one qualitative study a participant spoke of missing "*spontaneously getting together with other people. Because of my IBS, I don't dare follow sudden impulses to see other people anymore*" (Rønnevig et al., 2009). It seems that the more severe symptoms being experienced, the worse QoL individuals with IBS experience (Coffin, Dapoigny, Cloarec, Comet, & Dyard, 2004). If left untreated, symptoms of IBS fluctuate over time, but appear to persist rather than remit completely (Drossman et al., 2002; Canavan et al., 2014).

1.10 IBS Subtypes & Psychological Factors

1.10.1 Bowel pattern subtypes and psychological factors

As described above, IBS subtypes are predominantly characterised by bowel patterns (Drossman, 2016). The rationale for this is that there are different pharmacological treatments that can be prescribed according to the predominant bowel symptom patterns. The clinical merits of subtyping IBS by bowel pattern appear to end here and the tradition of doing so is one of contention (Talley, Zinsmeister, & Melton III, 1995; Whitehead, Palsson, & Jones, 2002; Marquis et al., 2014). Arguably, subtypes in IBS might be more clinically meaningful if they were found to either be associated with other clinical factors (such as symptoms, co-morbidities, psychological profiles) or impact upon clinical outcomes differentially. In terms of impacting on clinical outcomes, there is no compelling evidence to suggest that outcomes are worse in any particular IBS subtype (Muscatello et al., 2010). Qualitative research can however provide an insight into how differential bowel pattern subtypes in IBS may impact on psychological factors. Such research has found that while IBS-D is associated with feelings of urgency, IBS-C is associated with feeling incomplete evacuation and tendencies to strain on the toilet (Casiday et al., 2008; Rønnevig et al., 2009; Marquis et al., 2014; Fehnel et al., 2017). IBS-A is associated with both types of bowel sensations and all of the subtypes are associated with abdominal pain (Fehnel et al., 2017). The impact that urgency in IBS-A and IBS-D has is one of a sense of unpredictability and uncertainty, which can cause considerable stress and anxiety (Casiday et al., 2008; Rønnevig et al., 2009; Fehnel et al., 2017). For individuals with IBS-C, researchers have suggested that it is a sense of fear regarding the long-term damage of both constipation and the medications used to counteract it that is the issue (Casiday et al., 2008). Those with IBS-A have the potential to be affected by issues arising in both IBS-C and IBS-D. Qualitative research describes the different types of behaviours that the different

subtypes might engage in. Those with IBS-D may be prone to avoiding travel or social events due to fear of accidents (Casiday et al., 2008) as well as abstain from certain foods (Rønnevig et al., 2009). Furthermore they reported preparing for potential symptoms by taking anti-diarrhoea medications or wearing protection in their underwear (Rønnevig et al., 2009). Those with IBS-C also took precautions such as taking laxatives to prevent constipation. However the decision of whether they should was reported to be a difficult one with additional considerations (Rønnevig et al., 2009).

Some researchers have started to quantitatively address the question as to whether these bowel pattern subtypes are differentially associated with psychological factors (Prior, Maxton, & Whorwell, 1990; Farnam, Somi, Sarami, Farhang, & Yasrebinia, 2007; Eriksson, Andrén, Eriksson, & Kurlberg, 2008; Sugaya & Nomura, 2008; Muscatello et al., 2010; Stengel et al., 2010; Thijssen et al., 2010; Fond et al., 2014; Rey de Castro, Miller, Carruthers, & Whorwell, 2015; Kibune-Nagasako, Garcia-Montes, Silva-Lorena, & Aparecida-Mesquita, 2016; Polster et al., 2017). Relatively speaking, there are not many studies investigating this and the findings are contradictory. Most studies have focused on affective differences such as differences in anxiety or depression (Prior et al., 1990; Farnam et al., 2007; Eriksson et al., 2008; Sugaya & Nomura, 2008; Muscatello et al., 2010; Thijssen et al., 2010; Fond et al., 2014; Rey de Castro et al., 2015; Kibune-Nagasako et al., 2016). A meta-analysis of anxiety and depression comorbidities in IBS concluded that there were inconsistent findings as to whether the subtypes are differentially associated with anxiety and depression (Fond et al., 2014). This is likely to be because while some studies find that anxiety and/or depression is higher in one particular subtype, other studies find the opposite. Furthermore some studies investigating this reported no significant differences between groups (Rey de Castro et al., 2015).

There are even fewer studies assessing the difference in illness-related cognitions. All studies that have assessed these differences, have found no significant differences between subtypes (Sugaya & Nomura, 2008; Stengel et al., 2010; Thijssen et al., 2010). There appear to be even fewer studies assessing behavioural differences between subtypes, with one study finding that those with IBS-D reported more avoidant behaviour and agoraphobic symptoms than those with other IBS subtypes (Sugaya & Nomura, 2008). Another study assessed whether healthcare seeking behaviour differed across subtypes and found that it did not (Talley et al., 1995). These studies however were limited by small sample sizes, reducing the potential power to detect significant differences. Furthermore different studies utilised different tools for classification of

bowel symptom subtypes and not all studies included comparison of IBS-A in addition to IBS-C and IBS-D (Sugaya & Nomura, 2008). This therefore makes meaningful consolidation and comparison of such studies difficult.

Some researchers have progressed a step further than looking at existing subtypes and singular associations with various outcomes and psychological factors. Instead, they have assessed whether more encompassing subgroups exist within IBS, characterised by a range of symptomatic and psychological factors (Guthrie et al., 2003; Polster et al., 2017). Different statistical approaches were used to assess the existence of subgroups in IBS, and different measures were included to identify subgroup classification. Both studies identified that bowel patterns were still distinguishing features, but that these were differentially associated with psychological profiles and severity of symptoms. The first study identified three groups (1) high rectal sensitivity, high rates of sexual abuse history, psychiatric history, interpersonal problems and doctors visits (2) high rectal sensitivity, low rates of sexual abuse history and moderate psychiatric history (3) low rectal sensitivity, IBS-A or IBS-C, and low rates of doctor consultations and sexual abuse (Guthrie, et al., 2003). In contrast the other study found six subgroups that were more heavily characterised by bowel pattern subtypes. These included IBS-A, IBS-C and IBS-D with either high or low comorbidities of extra-intestinal somatic and psychological symptoms (Polster et al., 2017). These studies indicated that the characterisation of IBS subgroups may be more clinically meaningful with the inclusion of psychosocial factors.

1.10.2 Co-morbidities in IBS

It is well established that there is a higher rate of anxiety and depression amongst those with IBS (Drossman et al., 2002; Whitehead et al., 2002; Tanaka et al., 2011; Van Oudenhove et al., 2016). It was estimated that in up to 94% of IBS cases, psychiatric disorders such as major depression, anxiety and somatoform disorder also occurred (Whitehead et al., 2002). This review, along with others (Fond et al., 2014; Lee et al., 2017) found that the levels of anxiety and depression were particularly high in IBS when compared to healthy controls. The prevalence of anxiety and depression in FGIDs is between 30% - 50% and around 30% respectively (Van Oudenhove et al., 2016). It is not clear the extent to which such comorbidities have a causative role in IBS, or are the result of the symptoms and impaired functioning experienced in IBS. However, the coexistence of these comorbidities has been shown to negatively impact on illness trajectories, treatment outcomes GI symptom burden and health related quality of life (Lackner et al., 2014; Vu, Kushnir, Cassell, Gyawali, & Sayuk, 2014; Creed, 1999;

Drossman, 1999; Creed et al., 2005). The experience of psychological distress can lower pain threshold (Drossman et al., 2002; Drossman, 2005), exacerbate the experience of symptoms (Van Oudenhove et al., 2016) and increase healthcare seeking (Addolorato et al., 1998; Hu et al., 2002). Indeed such is the clinical importance of these psychiatric comorbidities, that researchers are increasingly suggesting that they should be factored into the classification of subgroups in IBS (Whitehead et al., 2002).

It has also been suggested that somatic comorbidities are considered in the subgrouping of IBS, as these can have important bearing on therapeutic formulation and processes (Reidl et al., 2008). Individuals with IBS who have one or more somatic comorbidity also report higher levels of anxiety and depression (Walker, Gelfand, Gelfand, Green, & Katon, 1996; Novi et al., 2005). This represents a significant proportion of those with IBS, as a systemic analysis of studies identifying the presence of somatic comorbidities in IBS found a twofold increase of these in IBS compared to controls (Riedl et al., 2008). Almost half of individuals with IBS were found to experience additional GI disorders such as gastroesophagul reflux disease or functional dyspepsia (Reidl et al., 2008). A broad range of extraintestinal comorbidities were also found to occur in up to 65% of IBS patients. These included fibromyalgia, chronic pelvic pain and chronic fatigue syndrome. The occurrence of one or more comorbidities was associated with increased health care utilisation (Whitehead et al., 2002; Riedl et al., 2008; Tanaka et al., 2011)

1.11 Economic Burden of IBS

IBS is estimated to cost the UK National Health Service (NHS) £45.6 million per year (Inadomi, Fennerty, & Bjorkman, 2003). There are a number of factors impacting on the health care costs of IBS. The first of which is the over reliance of diagnosis by exclusion (Yawn et al., 2001), with only 19% of those formally diagnosed with IBS having been given a diagnosis on their first visit (Hungin et al., 2003). Individuals with IBS also tend to visit physicians more than the general population (Talley et al., 1995; Camilleri & Williams, 2000; Inadomi et al., 2003). One study found that in a sample of 257 patients with severe IBS, the average amount of visits in a 6 month period was 6.9 (Creed et al., 2001). Furthermore, as briefly acknowledged earlier, the presence of comorbidities in IBS increases the utilisation of healthcare services (Whitehead et al., 2002; Riedl et al., 2008; Tanaka et al., 2011). Aside from the cost to health services, there is also an economic cost of IBS due to the number of sickness days taken by those with IBS (Hungin et al., 2003; Inadomi et al., 2003). In an assessment of the impact of IBS using

a community sample of over 40,000 participants it was found that on average individuals with IBS had 5.5 sick days compared with 3.1 days for those without IBS (Hungin et al., 2003). Individuals with IBS also averaged 10.2 days when work had to be cut short compared to 4.8 days without IBS (Hungin et al., 2003). The exact indirect costs arising from IBS in the UK are not clear but the total indirect costs for the US were estimated to be $205 million annually (Inadomi et al., 2003).

Consideration of the factors contributing to the economic cost of IBS is therefore important to identify ways to reduce it. A key area for reducing cost lies within the diagnostic procedures for IBS as increasing positive diagnosis and decreasing the use of diagnosis by exclusion can reduce healthcare costs. Improvement of diagnostic criteria to include more clinical markers in addition to bowel pattern classifications (e.g. somatic and psychological comorbidities) may increase GPs' confidence in providing diagnoses of IBS (Whitehead et al., 2002; Spiegel et al., 2010; Polster et al., 2017). Poor diagnostic procedures and subsequent communication HCPs provide to individuals with IBS has an economic impact due to the effect it has on health trajectories. Providing patients with a thorough understanding of their diagnosis and self-management options is important for improving illness trajectory (Owens et al., 1995; Casiday et al., 2008; Mira et al., 2015). Furthermore, thoroughly exploring the impact and role of comorbidities can reduce the future reliance on health care services (Johansson, Farup, Bracco, & Vandvik, 2010). One of the key frustrations of patients with IBS is the lack of "expertise" in IBS of physicians and the lack of information given to the patient (Owens et al., 1995; Casiday et al., 2008; Mira et al., 2015).

1.12 Treatment Approaches to IBS

There are different available approaches to treating IBS, both pharmacotherapeutically and psychologically (Drossman et al., 2002; Ford, Talley, Schoenfeld, Quigley, & Moayyedi, 2009). Individuals may also seek to treat IBS through a change in diet (Heizer, Southern, & McGovern, 2009) or with the use of probiotics (Hoveyda et al., 2009), discussion of which is beyond the scope of this thesis. Generally individuals with IBS who have milder symptoms (Drossman et al., 2002) or are in the early onset of symptoms (Yawn et al., 2001) treat their symptoms with pharmacological agents directly targeting the gut. These include the use of laxative agents and antidiarrheals. Long term use of these are not recommended due to the disruption to colonic motility if taken repeatedly (Saha, 2014). Antispasmodics are used in IBS to alleviate abdominal pain and have been shown to have good efficacy in doing so (Spiller et al., 2007; Ford et

al., 2008). The rationale for using such agents is to attenuate the increased contractions within the bowels seen in IBS, especially postprandially (Spiller et al., 2007). Antispasmodics do not however have an effect on bowel symptoms such as constipation or diarrhoea. In the UK only two of the antispasmodics shown to have efficacy are licensed. These are mebeverine and hyoscine (Spiller et al., 2007).

For individuals with more persistent and severe symptoms, additional symptoms may be prescribed or suggested by healthcare professionals. These include the use of psychopharmacology and psychological therapies, which are described below with consideration of the potential mechanisms of treatment effect.

1.12.1 Pharmacological treatment

1.12.1.1 Tricyclic Antidepressants (TCAs)

The use of TCAs in IBS has more established benefit than the use of SSRIs (Drossman et al., 2002; Ford et al., 2009; Ford et al., 2014). When prescribed for IBS, the dose is lower than when prescribed for depression or mood disorders. The lower dosage works quicker as a central analgesic, than when prescribed for depression in higher dosages (Drossman et al., 2002). Even with low doses however, side effects include constipation along with dry mouth, drowsiness and fatigue. As such it has been suggested that TCAs may be more beneficial to individuals with IBS-D as opposed to those with IBS-C (Spiller et al., 2007). As TCAs have a cumulative effect, healthcare practitioners are advised to communicate with patients that at least four weeks of taking the medication is needed to establish potential benefit (Spiller et al, 2007).

Exactly how TCAs exert analgesic effects in IBS is not currently understood. It is speculated that TCAs may work peripherally, by reducing visceral afferent activity directly in the GI tract, or centrally by facilitating inhibitory pain pathways (Chen, Ilham, & Feng, 2017). The alteration of pain perception is observed independently of their antidepressant and antianxiety effects (Clouse & Lustman, 2005).

1.12.1.2 Selective Serotonin Reuptake Inhibitors (SSRIs)

In contrast to TCAs, SSRIs accelerate intestinal transit (Clouse & Lustman, 2005) and therefore may be better used in the treatment of those with IBS-C. SSRIs are prescribed in their full psychiatric dose (Clouse, 2003) and therefore are superior to TCAs in treating the associated emotional symptoms of anxiety and depression (Drossman et al., 2002; Creed, 2006). It is the efficacy in decreasing psychological distress that is

hypothesised to be the predominant mechanism by which SSRIs have effect on enhancing global outcomes in IBS (Drossman et al., 2002; Clouse, 2003; Creed, 2006; Spiller et al., 2007). This is particularly so as although global improvements in over all health related quality of life are reported, generally bowel symptoms are unchanged (Spiller et al, 2007). There is less evidence that SSRIs have analgesic effects particularly in comparison to the evidence showing the analgesic effects of TCAs (Creed, 2006).

1.12.1.3 Anxiolytics

Anxiolytic medications such as benzodiazepines are sometimes prescribed in IBS where there is comorbidity of anxiety disorders, due to the recognition that acute psychological distress can make bowel symptoms worse (Drossman et al, 2002). Evidence of the efficacy of such drugs however is limited and it is not understood if the effects are centrally or peripherally mediated (Drossman et al., 2002; Salari & Abdollahi, 2011). There is also the potential problem of dependence and abuse of such medications, which can have strong physical withdrawal syndrome effects (Lader, 1994).

1.12.2 Psychological treatment

A number of psychological approaches to treating IBS have been reviewed in recent years showing a beneficial effect of hypnotherapy, psychodynamic interpersonal therapy, mindfulness and cognitive behavioural therapy (Ford et al., 2009; Ford et al., 2014). The treatments, evidence and potential mechanisms are described below.

1.12.2.1 Hypnotherapy

Hypnotherapy used in IBS is called "gut-directed hypnotherapy" (GDH). It involves the use of muscular and mental relaxation techniques and hypnotic suggestions to focus on symptoms or to distract from them (Webb, Kukuruzovic, Catto-Smith, & Sawyer, 2007). The hypnotherapist utilises feedback from the individual to further adapt suggestions to allow the individual a greater feeling of influence over symptoms (Whorwell, Prior, & Faragher, 1984; Moser et al., 2013). For example individuals may be asked to imagine the normalisation of GI function, using imagery of a blocked river clearing or flowing smoothly. Sessions are designed to provide individuals with a sense of control over external stimuli (such as the pressure of the chair, sounds, lights) and internal physiological experiences such as breathing and eventually bowel symptoms. Hypnotherapy in IBS is found to generally be effective in reducing pain and enhancing QoL (Wilson, Maddison, Roberts, Greenfield, & Singh, 2006; Webb et al., 2007; Miller et al., 2015). The quality of such studies has however been described as inadequate, with

a need for more high quality trials (Wilson et al., 2006; Webb et al., 2007; Rutten, Reitsma, Vlieger, & Benninga, 2013).

The precise mechanism/s of action in GDH has not been established, yet a number of possibilities have been proposed (Tan, Hammond, & Gurrala, 2005; Spiller et al., 2007; Rutten et al., 2013). It has been observed by researchers that hypnotic suggestion can change gastric motility (Whorwell, Houghton, Taylor, & Maxton, 1992; Houghton, Calvert, Jackson, Cooper, & Whorwell, 2002). However it is not clear whether this effect persists once an individual is no longer in a hypnotic state. In addition there is limited evidence showing other physiological change such as CNS/ANS activity or altered pain thresholds as a result of GDH (Tan et al., 2005; Spiller et al., 2007; Rutten et al., 2013). There is comparatively more evidence for the effect of GDH on potential psychological mediators (Rutten et al, 2013). Somatisation, psychological stress and negative cognitions have all been shown to reduce after GDH (Spiller et al., 2007; Rutten et al., 2013). The authors of one particular study that found symptom improvement after GDH was associated with a reduction in negative cognitions, suggested that the hypnotherapeutic approach to IBS may be considered a form of cognitive restructuring (Gonsalkorale, Toner, & Whorwell, 2004).

1.12.2.2 Psychodynamic interpersonal therapy

Psychodynamic therapy for IBS is referred to as "psychodynamic interpersonal therapy" (PIT) as it targets distress arising from interpersonal relationships, which are said to be the underlying cause of somatic symptoms (Guthrie, 2002). The treatment model asserts that individuals with IBS are submissive and seek reassurance from others (Hyphantis, Guthrie, Tomenson, & Creed, 2009). However, there is little evidence to suggest that these are qualities that characterise the entire heterogeneous IBS population. There is limited evidence coming from RCTs of PIT or the efficacy of PIT in IBS (Altayar, Sharma, Prokop, Sood, & Murad, 2015). The one RCT of PIT in IBS included participants with severe IBS and compared the efficacy of PIT to administration of an SSRI, paroxetine or treatment as usual (TAU) (Creed et al., 2003). Although superior to TAU, there were no significant differences between the efficacy of paroxetine and PIT in improving symptom severity or QoL. However, in the year follow up individuals who received PIT had a lower associated heath care cost than those in the SSRI group. Although this demonstrates a potential benefit of treatment, it is not clear whether this is the result of PIT specifically, or the opportunity for individuals to discuss their symptoms and feel heard. This has previously been shown to reduce the utility on

healthcare services (Owens et al., 1995; Inadomi et al., 2003; Johansson et al., 2010; Mira et al., 2015).

1.12.2.3 Mindfulness

There is increasing RCT-based evidence for the efficacy of mindfulness in IBS (Lakhan & Schofield, 2013; Zernicke et al., 2013). It is suggested that mindfulness may improve symptoms in IBS through the reduction of hypervigilance as individuals increase attentional control and reduce GI related anxiety (Garland et al., 2012). Studies assessing the efficacy on symptom severity and quality of life have found significant improvements compared to active and wait list controls (Ljótsson et al., 2010; Gaylord et al., 2011; Zernicke et al., 2013).

Mindfulness used in IBS is adapted from the traditional 8-week mindfulness based stress reduction programme (Kabat-Zinn, 1982) and delivered in groups. The mindfulness protocols tend to include a psycho-education component specifically regarding the physiology of IBS and the brain-gut connection. Guided meditations are used to alter individuals' relationships with their body and symptoms. Individuals are required to complete home practice, which consists of a meditative practice 6/7 days and/or an activity designed to increase awareness and break unhelpful cycles (e.g. a pleasant events diary, where individuals are asked to log 10 daily pleasant events). Adherence to home practice is hard to verify (Zernicke et al., 2013) but class attendance was generally good (Lakhan & Scholfield, 2013).

1.12.2.4 Acceptance and Commitment Therapy in IBS

Acceptance and Commitment Therapy (ACT) is a 'third wave' behavioural therapy, which conceptualises psychological inflexibility as a key factor in the maintenance and perpetuation of psychopathology (Hayes & Strosahl, 2004; Bravo Ferreira, Eugenicos, Graham Morris, & Gillanders, 2011). Psychological inflexibility is defined as the 'inability to modulate behaviour in response to how helpful it is' (Hayes & Strosahl, 2004). Increasing psychological flexibility therefore increases the capacity of clients to stay with experiences within the present moment and their ability to choose courses of action that are in line with their core values (Arch & Craske, 2008; Bravo Ferreira et al., 2011). The use of ACT in IBS is relatively new, with only two small pilot studies conducted to date (Ferreira, Gillanders, Morris, & Eugenicos, 2017). Although these showed positive changes in acceptance and symptom severity, both studies were limited by low power. Furthermore, the treatments assessed were not full courses of ACT

tailored for IBS, but rather a one-day group workshop with a self-help manual (Ferreira et al., 2017) and an ACT based psychoeducation self-management programme without therapeutic support (Ferreira et al., 2017). As such conclusions about the efficacy of ACT in IBS cannot be made at this stage.

1.12.2.5 Cognitive behavioural therapy

There is a substantial amount of good quality evidence coming from RCTs showing that CBT is effective for reducing symptom severity and enhancing QoL in IBS (Ford et al., 2009; Ford et al., 2014). CBT treatments for IBS involve cognitive restructuring, behavioural activation and exposure and psycho-education into the link between cognitions, behaviours, emotions and bowel symptoms (Toner et al., 2000). There are some differences in the treatments provided across different studies, which are described further below. These are considered in terms of the potential mechanisms involved in the different CBT treatment models.

1.13 Cognitive Behavioural Models of IBS

There are a number of cognitive behavioural models, which have slightly different formulations (Windgassen et al., 2017). All models share the hypothesis that biopsychosocial factors as described previously, have predisposing, precipitating and perpetuating role in IBS (Toner, Segal, Emmott, & Myran, 2000). More specifically the models focus on the perpetuating factors, all of which identify the role of cognitions and behaviours. Furthermore, all models suggest that it is GI-related cognitions and behaviours that are important in IBS (Toner et al., 2000), as opposed to more generic tendencies to catastrophise or act in response to emotion. The general goal of CBT for IBS is to allow individuals to reconceptualise their symptoms, shifting perceptions of lack of control to more optimistic controllable views of their symptoms (Toner et al., 2000). What distinguishes the models from each other is the differential focuses they place on particular perpetuating factors that are considered important for changing outcomes (i.e. symptom severity and QoL) in IBS. Each model is considered further below.

1.13.1 Three systems model

The three systems model was first proposed by Lang in relation to fear responses (Lang, 1968). The theory identified three response systems to fear: physiological reaction, overt-behaviour and cognitions. This three systems approach to IBS therefore focuses on the interplay between unhelpful illness-related cognitions, behavioural responses to

symptoms and physical sensations, which may pertain to the bowel symptoms themselves or the physical sensations of anxiety that may be associated with the experience of such bowel symptoms (Kennedy et al., 2005; Everitt et al., 2015). The model depicted in figure 1.3 shows how when an individual experiences bowel symptoms, they also experience anxious thoughts about the symptoms. Thoughts such as "*it will be embarrassing if I have an accident*", or "*I can't cope with these symptoms*" cause and are exacerbated by behavioural responses to symptoms (Beesdo-Baum et al., 2012). These behavioural responses may be avoidant (avoiding certain foods or activities to prevent or deal with symptoms). They may also reflect efforts to control symptoms. These are termed "safety behaviours" by clinicians and may include tendencies to take preventative medications, strain to pass a stool or wear protective underwear/loose clothing. Both cognitive and behavioural responses can have the effect of exacerbating or prolonging symptoms (Drossman et al., 2000; Rutter & Rutter, 2002; Lackner, 2005; Spence & Moss-Morris, 2007; Weinland et al., 2010). The key mediators of treatment effect proposed by this model are therefore GI related cognitions and behaviours. These have been shown to directly affect gut motility via the CNS (Kennedy et al., 2012) and indirectly. For example safety behaviours such as over-reliance on antimotility or laxatives to prevent feared symptoms can indirectly impact gut motility. This is because prolonged use can disrupting normal motility further or cause abdominal pain (Quigley et al., 2006; Rønnevig et al., 2009; Saha, 2014). Further consideration of mechanisms of psychological treatment in IBS is provided in chapters 3 - 5.

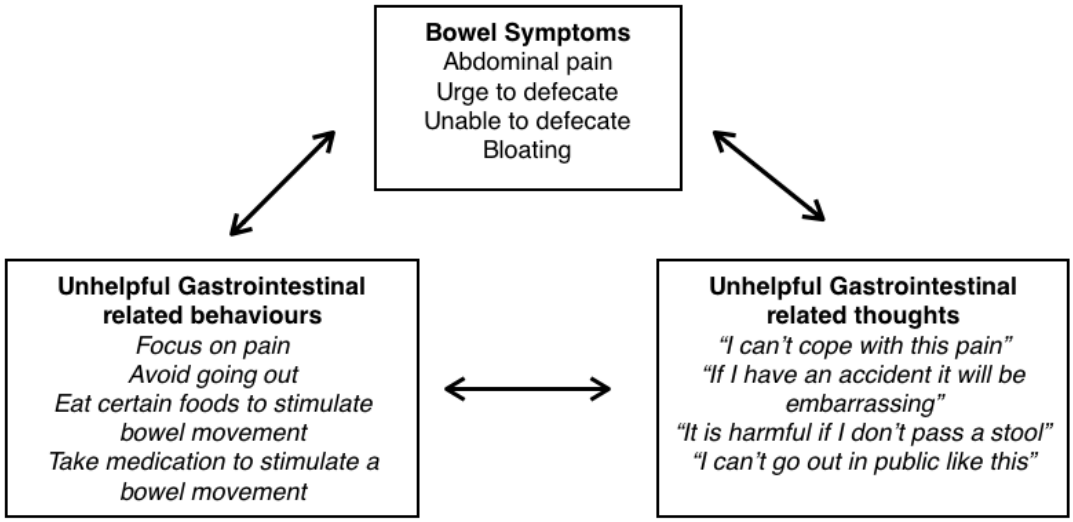

Figure 1.3: Three systems CBT model of IBS

1.13.2 Four factor model

The four factor CBT model of IBS includes the additional factor of emotion (Jones, Koloski, Boyce, & Talley, 2011). Figure 1.4 depicts how emotions such as anger and frustration impact on cognitions, behaviours and symptoms. The premise of the four factor model is that psychological treatments work by reducing the impact of disturbed emotional processing in the CNS, on gut function through management of stress and anxiety (Jones et al., 2011). The primary target for change in such therapy is therefore a reduction in anxiety/psychological stress. It is also important to distinguish the fact that the cognitions and behaviours targeted are therefore not always necessarily symptom related and may pertain to general responses to stress and anxiety.

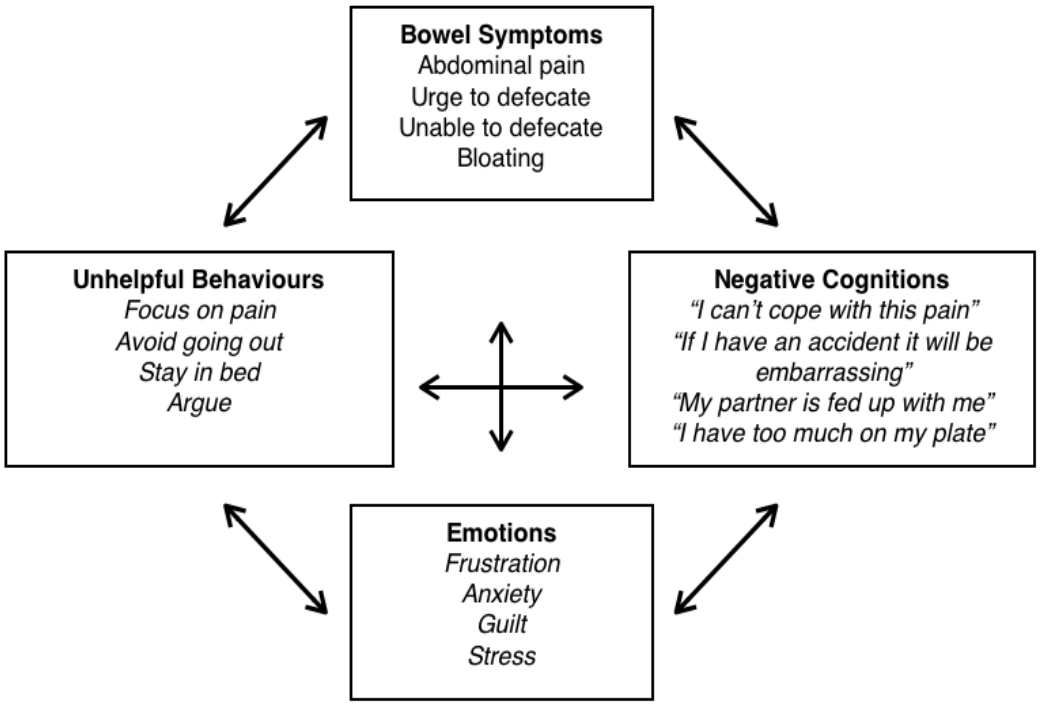

Figure 1.4: Four factor CBT model of IBS

1.13.3 Interoceptive exposure CBT model

More recently an interoceptive exposure CBT model (CBT-IE) was proposed to specifically target GI specific anxiety in IBS (Craske et al., 2011). GI specific anxiety (also called 'visceral anxiety') refers to the anxiety individuals have with regards to the anticipation and experience of GI symptoms (Mayer, Craske, & Naliboff, 2001). It has

been proposed that IBS symptoms are primarily affective in nature and risk factors such as general anxiety, neuroticism and worry/stress have an effect on symptom severity (Labus et al., 2005). The CBT models informing treatment target GI specific anxiety. This is based on the model of CBT used in panic disorder (Craske & Barlow, 2006). The model is depicted in figure 1.5, which shows that fear of gut sensations contributes directly to the intensity of such symptoms via the BGA. In addition GSA results in people with IBS trying to avoid gut sensations (e.g. by avoiding certain foods or tight clothing) and situations in which bowel symptoms may cause embarrassment or inconvenience (e.g. long journeys, restaurants with long delay/route to the bathroom). GI specific anxiety, avoidance behaviours and cognitions interact to maintain symptoms. Treatment involves exposure to visceral sensations (e.g. by tightening the stomach muscles) and feared situations, cognitive restructuring, attentional control training to reduce hypervigilance and psycho-education about the brain and the gut. As such, although the model differs slightly with a highly specific target of reducing GI specific anxiety, the treatment is very similar to that of the three systems approach.

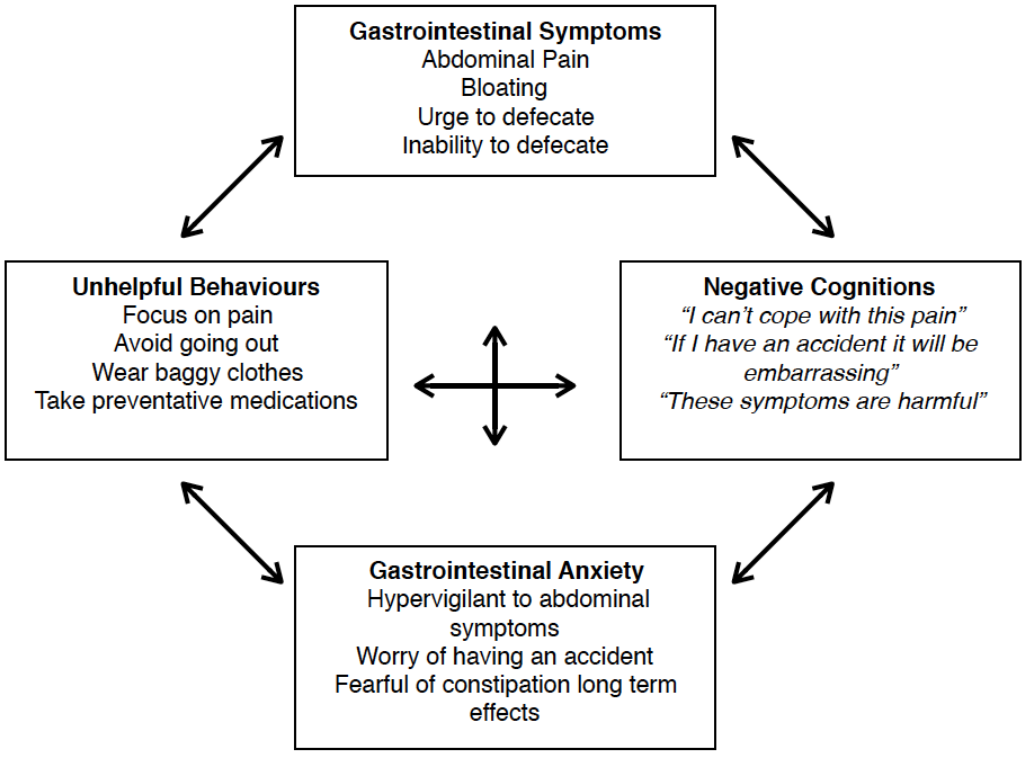

Figure 1.5: Gastrointestinal specific CBT model of IBS

1.14 Summary

IBS is a highly prevalent functional gastrointestinal disorder characterised by abdominal pain and altered bowel patterns. Four subtypes with IBS exist, characterised only by predominant bowel pattern: constipation predominant IBS (IBS-C), diarrhoea predominant IBS (IBS-D), alternating IBS (IBS-A) and unclassified IBS (IBS-U). There is limited and contrasting evidence that particular subtypes are associated with certain psychological characteristics. Researchers have called for more clinically meaningful subgroup classifications in IBS, which take into account levels of symptom severity, co-morbidities and other psychological characteristics.

IBS is a biopsychosocial disorder, with a clear pathophysiological mechanism by which psychosocial factors can affect bowel symptoms and gastrointestinal pain. Psychological treatments have been shown to be effective in reducing symptoms and enhancing QoL in IBS. CBT is the psychological approach with the most high quality empirical support. The mechanisms of treatment effect may vary depending on the specific CBT model being applied. Generally, cognitions, behaviours and affective factors such as anxiety/gastrointestinal related anxiety are identified as key targets for change.

2. Methodological Overview

2.1 Chapter Overview

The previous chapter introduced the importance of cognitive and behavioural factors in irritable bowel syndrome (IBS). The present thesis had two main objectives: (1) to assess whether cognitive and behavioural factors were mediators of treatment effect on the outcomes of symptom severity and work and social adjustment/quality of life (2) to identify cognitive and behavioural factors associated with IBS bowel pattern subtypes. To meet objective one, two studies were conducted consisting of a systematic review (study one) and a mediation analysis (study two) using data from a previously conducted randomised controlled trial comparing the antispasmodic, mebeverine, alone to cognitive behavioural therapy (CBT) plus mebeverine. To meet objective two, two further studies were conducted to assess differences in psychological factors between IBS bowel subtypes (study three and study four). Study three used the same data as study two, and study four used prospectively collected data from a randomised controlled trial assessing CBT in IBS.

This chapter will provide details of the study design of the two trials, before providing an outline of the methodology employed to complete the studies included in the thesis. This will include a chart depicting the sequence of studies and how they fitted with data collection.

2.2 The Cognitive Behavioural Therapy in Addition to Antispasmodic Treatment for Irritable Bowel Syndrome in Primary Care Trial

The Cognitive Behavioural Therapy (CBT) in Addition to Antispasmodic Treatment for Irritable Bowel Syndrome in Primary Care Trial was conducted prior to the beginning of this thesis, the results of which are reported comprehensively elsewhere (Kennedy et al., 2005; Kennedy et al., 2006). The data from this trial were used for secondary analysis in two studies contained in this thesis (2.4). An outline of the study design, intervention and measures utilised for the purposes of this thesis only, are detailed below. This data set shall be referred to as 'data set 1'.

2.2.1 Design

The study was a randomised controlled trial (RCT) comparing the effect of CBT in addition to the antispasmodic medication, mebeverine, to mebeverine alone on the outcomes of symptom severity and work and social adjustment in irritable bowel syndrome (Kennedy et al., 2005). Figure 2.1 depicts the CONSORT study flow diagram detailing the steps of recruitment and follow up assessments included in the study.

2.2.2 Participants and procedure

Individuals aged between 16 and 50, diagnosed with IBS and meeting the Rome I criteria (Thomson, Doleval, Drossman, & Heaton, 1989) were recruited from 10 London general practices. A total of 235 participants completed the initial assessment measures utilised in study three; 149 participants were randomised to either receive mebeverine alone (77) or to receive CBT in addition to mebeverine (72). The data for one participant was lost, leaving 148 participants to be included in analysis in study two.

Questionnaire measures were taken at 7 time points (figure 2.1), two of which occurred prior to randomisation (visit 1 and visit 2). The first assessment was conducted at screening and the second assessment was taken after two weeks of treatment as usual, once participants had consented to participate in the study. The baseline (start of RCT) measure was taken at visit 3 and the first follow up at 1.5 months post randomisation at visit 4. The second follow up was at 3 months (visit 5) and the ultimate follow up at 12 months (visit 7).

2.2.3 CBT intervention

The therapy was delivered in face-to-face sessions by four general practice nurses who had received training in CBT and were under the close supervision of an experienced therapist. Participants received six 50 minute sessions at weekly intervals. The CBT intervention was based on Lang's three systems model (Lang, Melamed, & Hart, 1970) as adapted for IBS, which posits that GI related cognitions and behaviours interact to maintain and exacerbate the experience of symptoms. To target GI cognitions and behaviours the intervention included psychoeducation, cognitive restructuring and behavioural techniques. The psychoeducation provided information about the physiology of the bowel and the brain-gut connection. Cognitive restructuring was aimed at making individuals aware of unhelpful gastrointestinal (GI) related thoughts, recognising how these affected their behaviours and GI symptoms. Patients were encouraged to challenge these thoughts and identify alternative thoughts. Behavioural techniques involved goal setting to increase helpful behaviours such as eating regular meals, regular exercise and drinking water, whilst reducing unhelpful behaviours. Behaviours identified as unhelpful could be avoidance behaviours such as avoiding situations that may be impacted by bowel symptoms, or safety (also termed 'control') behaviours such as taking precautionary measures like trying to force the bowels to empty before leaving the house. Techniques to manage stress and prevent relapse were also included. The treatment aimed to improve participants' ability to participate in life despite their IBS symptoms. It was anticipated that IBS symptoms may also reduce as a result of treatment. A summary of sessions is contained in appendix F.

2.2.4 Antispasmodic treatment

Individuals in both the CBT treatment arm and antispasmodic alone arm took 270mg of the antispasmodic, mebeverine, three times daily. Antispasmodics have been shown to be effective in reducing the global effect of IBS (Ford et al., 2008; Ruepert et al., 2011).

2.2.5 Measures

Primary outcome measures

The Irritable Bowel Severity Scoring System (IBS-SSS) (Francis, Morris, & Whorwell, 1997) measures symptom severity specific to IBS and is sensitive to change over time. The maximum score is 500, with scores <75 indicating normal bowel function. Scores between 75-174 indicate mild IBS, 175-299 moderate IBS and scores between 300-500

indicate severe IBS. A 50 point change from baseline is regarded as clinically significant (Francis et al., 1997).

The Work and Social Adjustment Scale (WSAS) (Mundt, Marks, Shear, & Greist, 2002) is a measure of work and social functioning. It contains 5 items each rated 0 - 8, with a total potential score of 40. The items assess individuals' ability to engage in day-to-day tasks at work, at home, socially, with family and in relationships. It was found to be a reliable and valid measure of impaired functioning with an internal scale consistency ranging from α 0.70 to 0.94 for the 5 subscales (Mundt et al., 2002).

'Illness Identity symptom' item from the Adapted Illness Perception Questionnaire (IPQ) to assess Bowel Pattern Subtype (Moss-Morris et al., 2002)

Predominant bowel pattern was identified through recoding of the adapted 'Illness Identity symptom' items of the Illness Perception Questionnaire (IPQ), which asked participants how often they experienced diarrhoea and constipation. Responses were rated as "never = 0", "occasionally = 1", "frequently = 2" or "all of the time = 3". Constipation predominant IBS was defined as individuals who never experienced diarrhoea and scored ≥1 for constipation. Diarrhoea predominant was defined as individuals who never experienced constipation and scored ≥1 for diarrhoea. Individuals who scored ≥1 for constipation and diarrhoea were classified as having alternating bowel pattern. Those who scored 0 for both diarrhoea and constipation were classified as IBS-U.

Secondary outcome measures

The Cognitive Scale for Functional Bowel Disorders (CSFBD) (Toner et al., 1998) contains items that assess thoughts specific to the experience of functional bowel disorders such as "*my bowel symptoms make me feel out of control*". The scale consists of 25 items, with a possible total score of 25 to 175 with higher scores indicating more illness-related cognitions. The measure has been demonstrated to have good reliability and validity α=0.93 (Toner et al., 1998).

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) contains two subscales measuring anxiety and depression and is well validated in different patient populations (Bjelland, Dahl, Haug, & Neckelmann, 2002). The anxiety and depression subscale of the HADS are each made up of 7 items scored from 0 to 3, with a total possible score of 21. Scores of 8 and above are said to indicate anxiety and depression (Bjelland et al., 2002). The anxiety subscale assesses general anxiety rather than anxiety

specific to IBS, with items such as "*I feel tense or wound up*" or "*worrying thoughts go through my mind*". The depression subscale includes items such as "*I feel as if I am slowed down*".

The IBS Behavioural Responses Questionnaire (IBS-BRQ) (Reme, Darnley, Kennedy, & Chalder, 2010) consists of two subscales. The first measures avoidance behaviour such as "*I avoid going out in case I have problems with my IBS*" (15 items). The second subscale assesses safety behaviours (11 items), which are referred to as 'control behaviours' in the scale. An example safety behaviour item is "*I spend more time on the toilet than I would ideally like*". Each item is scored on a scale of 1-7, and the two subscales are scored by summing the total of the items. Higher scores indicate higher levels of unhelpful behaviours. The scale has been shown to have good reliability and validity α=0.86 (Reme et al., 2010).

2.2.6 Power calculation

Power was calculated a priori to detect differences between the CBT + mebeverine group and the control group. The calculation assumed that the mean score (SD) on the IBS-SSS at six months' follow up would be 133 (80) in the CBT + mebeverine group and 180 (80) in the control group. To give the power 90% power, with 95% confidence it was indicated that 62 patients were needed in each group.

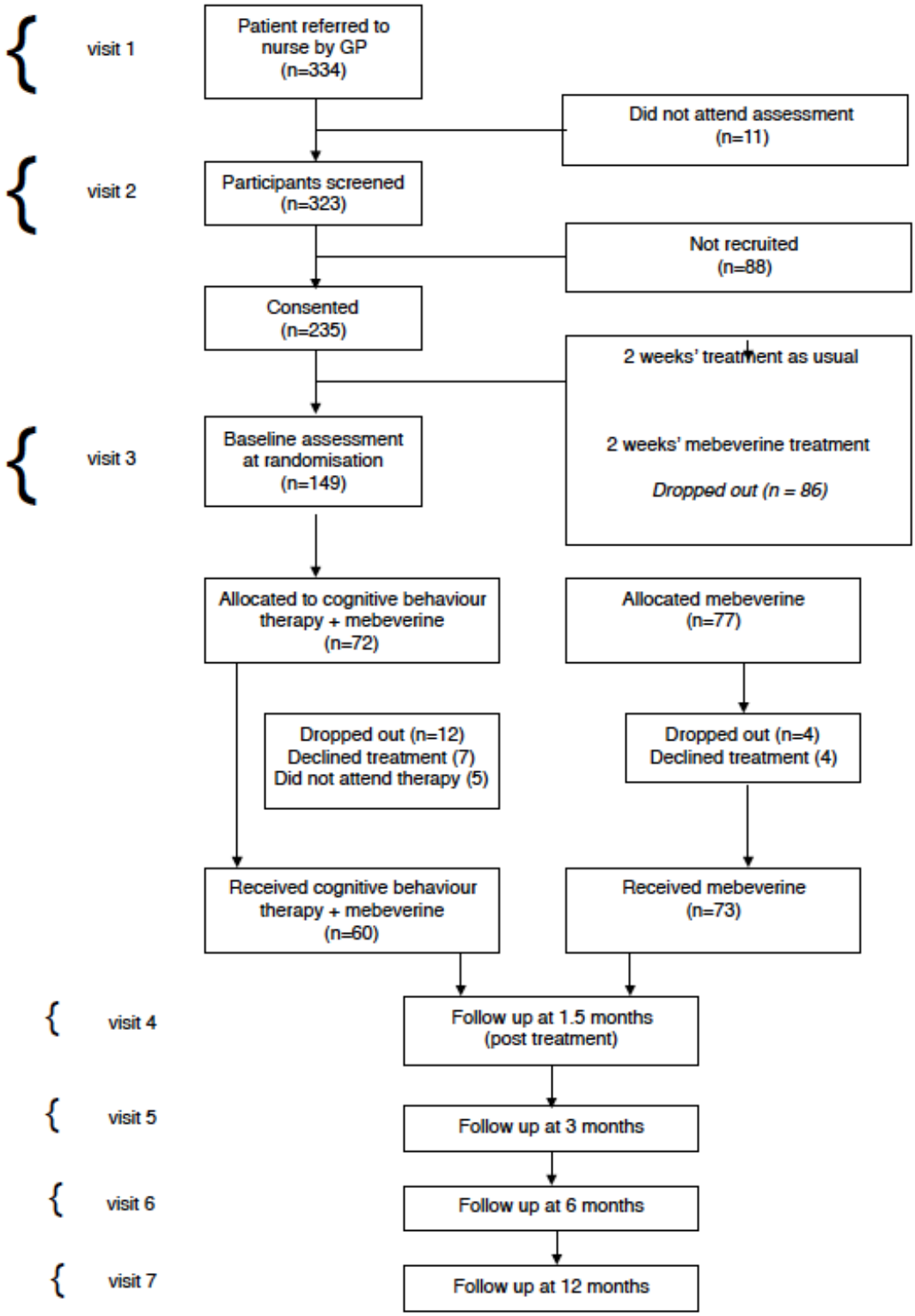

Figure 2.1: CONSORT diagram of the study design and data collection for The Cognitive Behavioural Therapy in Addition to Antispasmodic Treatment for Irritable Bowel Syndrome in Primary Care Trial

2.3 Assessing Cognitive Therapy in Irritable Bowel (ACTIB) Trial

The ACTIB Trial began concurrently with the beginning of the present thesis, allowing prospective data collection. The completion of data collection up until the 12 month follow ups occurred approximately nine months prior to the doctorate submission deadline and therefore it was only possible to utilise the baseline data in analysis conducted for the present thesis (2.4). The results of the study are pending, however the trial protocol has been published for further detail of the study design (Everitt et al., 2015). This data set shall be referred to as 'data set 2'.

2.3.1 Design

The ACTIB Trial was a RCT comparing three arms, consisting of two treatment arms and a treatment as usual (TAU) arm. The two treatment arms both included the same CBT intervention content, but delivered in different formats with different therapist time allocations. The 'Therapy CBT' (TCBT) arm was the high intensity group consisting of six x 60 minute phone sessions over a three month period, with two further follow up sessions in addition to TAU. In this arm participants were provided with a CBT booklet with eight chapters and homework exercises. In the 'Website Based CBT' (WBCBT) arm, participants received a low intensity CBT intervention, receiving three x 30 minute phone sessions over a three month period with two further follow up sessions in addition to TAU. Participants in this group predominantly worked through the CBT programme utilising an interactive online self-management programme, which contained the same information and exercises as the booklet provided in the TCBT arm. Those participants allocated to TAU were instructed to continue with their current medication and GP consultation follow ups, but asked not to engage in psychological therapy for IBS and to refrain from partaking in any other interventions for IBS. All treatment arms received a standard information sheet on lifestyle and diet in IBS, based on NICE guidelines (appendix E). The TAU participants had access to the WBCBT without the additional telephone support after completion of the 12 month follow up. Figure 2.2 shows the CONSORT flow diagram detailing the progression of participants through the trial.

2.3.2 Participants and procedures

Individuals aged 18 + with refractory IBS were recruited from primary and secondary care sites in South London and Hampshire. To meet the inclusion criteria participants had to meet the Rome III criteria for IBS (Drossman & Dumitrascu, 2006), have a

diagnosis of IBS for at least 1 year and score at least 75 on the IBS-SSS (Everitt et al., 2015). Participants had to have been offered first line IBS medications with persisting symptoms for at least 12 months. Participants of 60+ had to have had a review of their symptoms with a consultant in the last two years to confirm that their symptoms were related to IBS and to exclude the possibility of other more serious bowel conditions. This was due to the recommendations of NICE guidelines advising further investigation of new change in bowel habit in those 60 years and over due to the increased risk of bowel cancer in this age group (Hookway, Buckner, Crosland, & Longson, 2015).

Once participants were deemed to be eligible at the screening stage, they were asked to provide informed consent online. When consent was provided, potential participants were given instructions to get a blood test or retrieve results of blood tests completed within the last three months. The purpose of the blood tests was to exclude alternative diagnoses to IBS. The blood tests included a full blood count (FBC) for anaemia, transglutaminase antibodies (TTG) for Coeliac disease and C Reactive Protein (CRP) for inflammation, which can be a marker for inflammatory bowel disease. The Chief Investigator (CI) checked the blood results to determine eligibility. For patients with abnormal FBC or TTG results, participants were excluded from the study and referred back to their GP. CRP can be raised temporarily due to minor illness or infection therefore participants with an abnormal CRP were offered a second test after 4 weeks. Potential participants with a second high CRP result were excluded from the trial and their GP was informed of the test result.

Once potential participants received confirmation of normal blood tests, they completed baseline questionnaires online. After these were completed, participants were randomised to a treatment arm. 558 participants were successfully randomised and allocated to TCBT (n =186), WBCBT (n=186) or TAU (n=187). Questionnaire measures were assessed at 4 time points, which was then extended to an additional time point of 24 month follow up. The 24 month follow up data collection is due to be completed in June 2019.

2.3.2 CBT interventions

The content of the CBT included in both treatment conditions was the same and drew on therapy content from the previous trial (Kennedy et al, 2005; Kennedy et al, 2006), a self-management CBT programme designed for IBS (Moss-Morris, McAlpine, Didsbury, & Spence, 2010) and adapted parts of the CBT manuals used in a trial of therapies for chronic fatigue syndrome (White, Sharpe, Chalder, DeCesare, & Walwyn,

2007). The intervention utilised more of a four-factor approach than a three systems approach, identifying cognitions, behaviours and emotions as key maintaining factors of IBS symptoms (Everitt et al., 2015). The therapy consisted of psychoeducation about the physiology of the bowels and the connection with the brain. Cognitive and behavioural techniques were used to improve bowel habits and eating patterns, address unhelpful thoughts, manage stress, reduce symptom focusing and prevent relapse. A summary of the sessions is contained in appendix F. Ten therapists experienced in delivering CBT in medically unexplained and long-term conditions delivered the therapy in both treatment arms. All therapists received additional training in the CBT model for IBS and supervision was tailored specifically for IBS delivered via the telephone or through the internet.

2.3.2.1 Therapist cognitive behavioural therapy (TCBT)

Individuals randomised to TCBT were provided with a hard copy paper manual of the CBT programme consisting of eight chapters with allocated homework tasks (appendix F). Participants received six one-hour telephone sessions with their allocated therapist over a 9-12 week period and were encouraged to work through the manual in between sessions. Two one-hour 'booster' telephone sessions were arranged at around the four and eight month post randomisation point. Although based on the content of the sessions in the patient manual, the TCBT telephone sessions were formulation driven so that the order and extent to which all sessions were covered was individualised.

2.3.2.2 Website based cognitive behavioural therapy (WBCBT)

Individuals randomised to WBCBT were provided with a login to the online CBT intervention and advised to start working sequentially through the eight online weekly sessions and homework tasks. The formulation was completed online by participants using the interactive tools of the website to map out their own CBT model of IBS. Participants received weekly reminders to log in and complete sessions. In addition, they received three 30-minute telephone therapy support calls over 9-12 weeks and two more 30-minute booster sessions at around the four and eight month post randomisation point. These phone support sessions were deemed necessary to aid participant engagement with the programme. Limited therapist input has shown promising results in previous similar remote CBT based interventions for IBS (Hunt, Moshier, & Milonova, 2009; Ljótsson et al., 2010). When appropriate, therapists could use the phone calls to suggest that participants focus on particular sessions rather than others.

2.3.4 Treatment as usual (TAU)

Participants in all three arms received TAU, with TAU alone constituting the control arm of the trial. TAU was defined as the continuation of current medications and usual general practitioner (GP) or consultant follow-up with the exclusion of any psychological therapy for IBS. All GPs and consultants involved in the study received a copy of the NICE Guidance (appendix E) at the start of the study to ensure that they all had the best standard practice information on IBS management. Those participants that were allocated to TAU alone were provided with access to the WBCBT website at the end of the 12 month follow up period.

2.3.5 Measures

The measures used for the present thesis from the ACTIB data collection (data set 2) were the same as the ones used in data set 1 (Kennedy et al., 2005) with one exception. In data set 1, the adapted IPQ was used to classify bowel pattern subtypes, whereas in data set 2, the Rome III criteria was used. The Rome III was assessed at screening only and no at baseline or subsequent follow ups. All copies of the questionnaires used for the thesis can be found in appendix D.

Rome III Criteria (Drossman & Dumitrascu, 2006) to assess bowel pattern subtypes

The Rome III is a diagnostic tool for assessing IBS and identifying bowel pattern subtypes. Individuals were classified as IBS-D if they had lose/watery stools ≥ 25% of the time and had hard/lumpy stools < 25% of the time. IBS-C was defined as those with lose stools <25% of the time and hard stools ≥25%. IBS-A was categorised as those with both hard and loose stools ≥25% of the time, while IBS-U experienced hard and loose stools <25%

2.3.6 Power calculation

Power calculations were conducted a priori to determine necessary sample size for each condition to detect differences in the primary outcome. To achieve power of 90%, taking into account the number of therapists providing therapy and attrition rate, it was calculated that 165 participants were needed for each group, totalling 495 participants. This was increased to 189 per group as the attrition rate was found to be closer to 30% than the projected <20% rate, totalling a required sample size of 567.

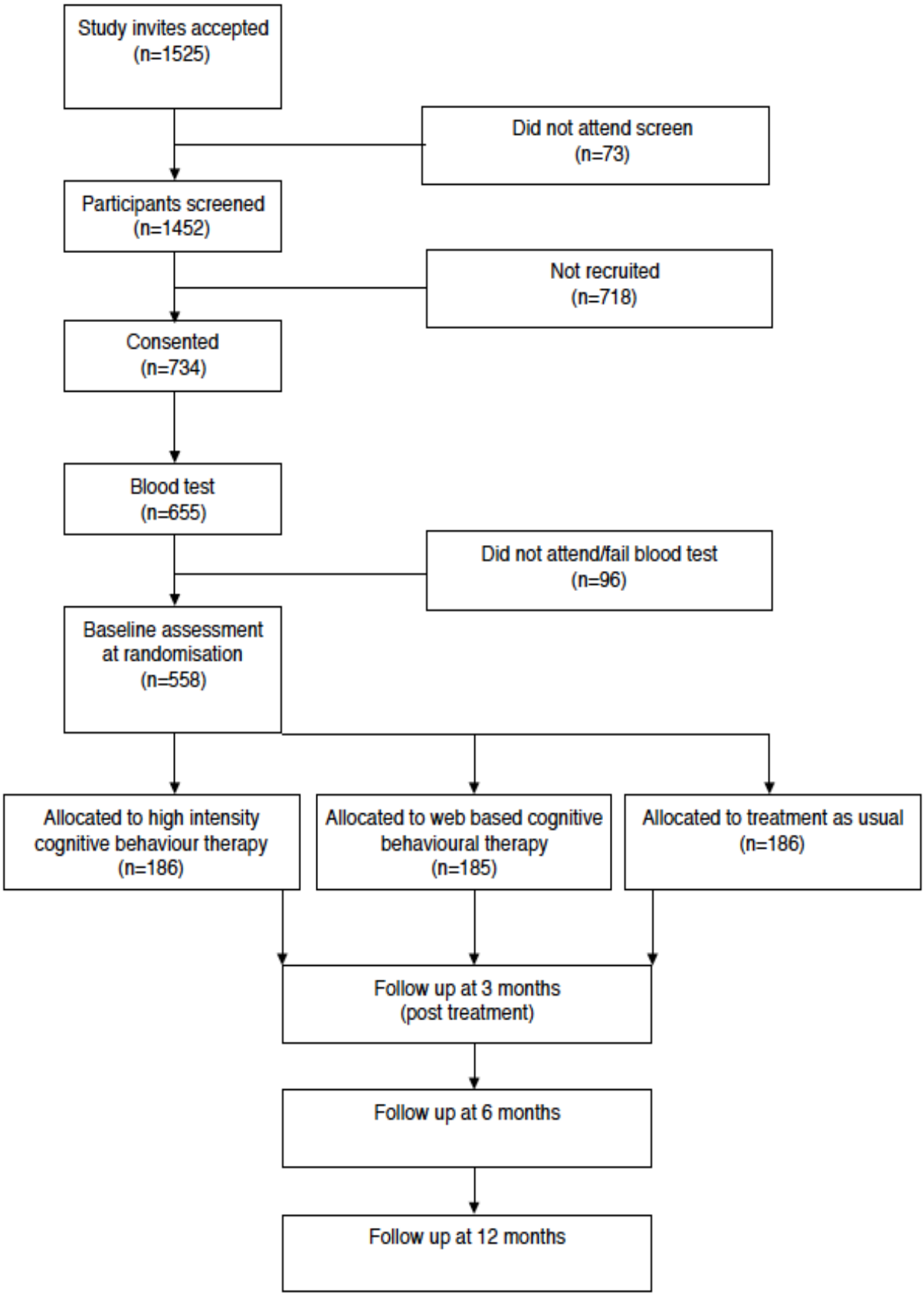

Figure 2.2: CONSORT diagram of the study design and data collection for The Assessing Cognitive Therapy in Irritable Bowel Syndrome

2.4 Study Sequence

2.4.1 Study aims and objectives

The two main objectives of the thesis were: (1) to assess whether cognitive and behavioural factors were mediators of treatment effect on the outcomes of symptom severity and work and social adjustment/quality of life, and (2) to identify cognitive and behavioural factors associated with IBS bowel pattern subtypes. Two studies (studies one and two) were conducted to assess aim one, and two studies (studies three and four) were conducted to address aim two (table 2.1, figure 2.3).

The more specific aim of study one was to systematically identify psychological factors found to mediate the effect of psychological interventions in IBS on the outcomes of symptom severity and/or quality of life. It was hypothesised that cognitions, behaviours and anxiety would significantly mediate treatment effect, in line with cognitive behavioural models of IBS (Kennedy et al., 2005; Craske & Barlow, 2006; Moss-Morris et al., 2010).

Study two had two more specific aims: (1) to assess whether GI related avoidance behaviours, GI related safety behaviours, GI related cognitions, and general anxiety mediated the effect of CBT on symptom severity and work and social adjustment, and (2) to identify which mediating variables changed first in sequential mediator models. It was hypothesized that all four variables would significantly mediate the effect of CBT on both symptom severity and work and social adjustment based on the theoretical treatment model and findings from previous studies (Windgassen et al., 2017). It was also hypothesized that cognitive and behavioural change would precede change in anxiety, as these were the targets for change in the treatment protocol informed by the three systems model. Furthermore, in the previous mediation study based on the same data, cognitive and behavioural change was found to precede changes in anxiety (Reme, Stahl et al, 2011).

Study three and four both aimed to assess whether there were differences in cognitive and behavioural factors in addition to levels of anxiety, depression, symptom severity and work and social adjustment across IBS subtypes. Study three had the additional aim of assessing whether abdominal pain was associated with specific bowel pattern subtypes. It was hypothesised that due to the nature of symptoms and the additional burden created by the experience of diarrhoea, those with IBS-A and IBS-D would have more extreme symptoms, disability and cognitive, behavioural responses compared to

those with IBS-C. This is due to the unpredictability and uncertainty of diarrhoea as opposed to constipation. With regard to the relationship between bowel pattern subtypes and abdominal pain, it was hypothesised that individuals with IBS-A and IBS-D would have higher levels of abdominal pain compared to IBS-C, based on previous findings assessing this association (Heitkemper et al., 2011).

Study four aimed to validate the findings from study three in a larger sample with bigger power to detect differences. It was hypothesised that cognitions and behaviours would differ between subtypes. Based on previous results, the three specific hypotheses were that (1) unhelpful cognitions would be greater in those with IBS-D than IBS-C, (2) unhelpful avoidance behaviours would be greater in those with IBS-D and IBS-A compared to IBS-C, and (3) control behaviours would not significantly differ across subtypes.

2.4.2 Study methodology

Precise details of the statistical analyses utilised in each study are provided in the respective chapters. This section will instead provide a rationale for the methods used in each study and how they fit the aims of the study.

2.4.2.1 Study one

This study aimed to assess psychological mediators of treatment effect in the context of psychological interventions for IBS. In order to systematically collate findings from previous research assessing mediation in such a context, it was decided that a systematic review should be used. Systematic reviews identify, appraise and synthesise findings from empirical studies conducted in a specified area of research (Littell, Corcoran, & Pillai, 2008). In contrast to narrative reviews, they reduce bias by identifying all available studies meeting a stipulated inclusion criteria, and systematically assessing the quality of the studies (Higgins & Green, 2011). This allows consideration of the results balanced against the relative quality of the study. The PRISMA guidelines ensure standardised reporting of the methodology and results of systematic reviews (Moher et al., 2015). These guidelines were adhered to in the systematic review presented in this thesis.

The alternative approach to a systematic review would have been a meta-analysis. A meta-analysis involves the use of statistical techniques to synthesize the data from several studies into an effect size (Littell et al., 2008). This approach was considered but determined to be inappropriate in the context of the mediation analysis studies returned

from the systematic review, for a number of reasons. The measures of indirect effects (mediated effects) were inconsistently reported, some papers only reported the effect sizes of the overall path model and not the composite mediating pathways, whether these were singular (i.e. one mediator pathways) or sequential (i.e. multiple mediators in a pathway). Furthermore, of those studies presenting the indirect effects, different measures of effect size were used, preventing the data from being pooled. In four out of eight studies, the data necessary to conduct a meta-analysis was not available. In addition, not all studies assessed the same mediators, resulting in very small pools of mediator variables to compare. On balance, the small number of studies returned allowed a meaningful review of the results without an additional meta-analysis, providing a good basis for informing and improving future studies.

2.4.2.2 Study two

Study two aimed to assess both simple mediation models (i.e. one mediator) and sequential mediation models. It was determined that structural equation modelling (SEM) was the best method available to conduct mediation analysis. SEM is sometimes referred to as path analysis when it is conducted using observed variables rather than latent variables (Mackinnon, 2008). Path analysis (or SEM) allows the modelling of multiple outcomes simultaneously (Mackinnon, Fairchild, & Fritz, 2007; MacKinnon, 2008; Bollen & Pearl, 2013). This means that longitudinal modelling of multiple measures of mediators and outcomes can be conducted, which enables the assessment of sequential mediation models as was required in the present study. For example, it allows the assessment of whether change in one mediator (mediator one) causes change in another mediator (mediator two), or whether this path is best explained in reverse; i.e. change in mediator two causes change in mediator one instead. This method of analysis also allows the inclusion of potential confounding variables in the analysis, controlling for the effects such variables may have on the relationships between other variables of interest (MacKinnon, 2008; Emsley, Dunn, & White, 2010). For this reason path analysis is superior to the traditional but somewhat out-dated alternative method of Baron & Kenny's causal steps framework (Baron & Kenny, 1986). This approach specifies that a number of regressions need to be conducted to establish whether mediation exists. These regressions are used to establish whether (1) the effect of the independent variable on the dependent variable is statistically significant, (2) the effect of the independent variable on the mediator is significant, (3) the effect of the mediator on the dependent variable is significant, and (4) the relationship between the independent variable and the dependent variable is no longer significant when

controlling for the mediator. It was postulated that this would indicate that the relationship between the independent and dependent variable was fully explained by the mediator variable. This approach does not allow for the modelling of sequential mediation models. This methodological approach to mediation is compared to path analysis further in chapter 6.

The original trial was not powered for mediation analysis and there is no existing literature that provides sufficient information on how to calculate power for more complex meditational models as were conducted in study four (Thoemmes, MacKinnon, & Reiser, 2010). However guidelines have been developed for suggested sample sizes to achieve 80% power for simple mediation models based on small, medium and large effect sizes of the α and β paths (Fritz & MacKinnon, 2007). The α path is the path from independent variable to the mediator and the β path is the path from the mediator to the dependent variable. For medium effect sizes (0.39) of both paths, a sample of 71 is necessary to detect mediated effects when applying the bias-corrected bootstrap as was done in study two (Fritz & MacKinnon, 2007). For an effect size halfway between small and medium (0.26) a sample size of 148 is needed (Fritz & MacKinnon, 2007).

2.4.2.3 Studies three and four.

Studies three and four both used one-way ANOVAs to assess differences in psychological variables and outcome measures between three IBS subtypes (IBS-A, IBS-C and IBS-D). IBS-U was excluded in both analyses because of the disproportionately low numbers of participants classified in this subtype. One-way ANOVAs were used to detect differences between groups as this analytical approach is the most commonly used technique for comparing group means (McDonald, 2009). In a one-way ANOVA there is one independent variable (e.g. group) and one dependent variable (outcome of interest). The analysis calculates the mean of the observations within each group then compares the variance across the group means to the average variance within each group. As the means get further apart, the variance among the means increases. The test statistic (F statistic) is therefore a ratio of the variance across the means divided by the average variance within the groups (McDonald, 2009; Pagano, 2012).

The two samples of data were analysed separately as they could not be pooled due to the use of different measurements of IBS bowel pattern subtypes. Furthermore it is good practice to assess patterns or associations in one data set and replicate in another to validate results (Mishler, 1990; Agrillo & Petrazzini, 2012).

A priori power calculations were not possible for study three or four, however post hoc power calculations were conducted for each study (chapter 7 and 8)

Table 2.1: Overview of studies

Study Number	Name of paper	Aim/s	Primary Analysis	Data set used	Chapter Reference
Objective 1					
Study one	The journey between brain and gut: A systematic review of psychological mechanisms of treatment effect in irritable bowel syndrome	To systematically identify psychological factors found to mediate the effect of psychological interventions in IBS on the outcomes of symptom severity and/or quality of life	Systematic review	NA	4
Study two	Key mechanisms of cognitive behavioural therapy in irritable bowel syndrome: the importance of gastrointestinal related cognitions, behaviours and general anxiety	(1) to assess whether gastrointestinal (GI) related avoidant and safety behaviours, GI related cognitions and general anxiety, mediated the effect of CBT on outcomes (2) to identify which mediating variables changed first in sequential mediator models	Mediation analysis (structural equation modelling)	Data set 1	5
Objective 2					
Study three	Behavioural differences between Irritable Bowel Syndrome subtypes & other psychological associations	To assess whether cognitive and behavioural factors in addition to levels of anxiety, depression, symptom severity, abdominal pain and work and social adjustment significantly differed across IBS subtypes	One-way ANOVA	Data set 1	7
Study four	Cognitive and behavioural differences between irritable bowel syndrome subtypes	To assess whether cognitive and behavioural factors in addition to levels of anxiety, depression, symptom severity and work and social adjustment significantly differed across IBS subtypes	One-way ANOVA	Data set 2	8

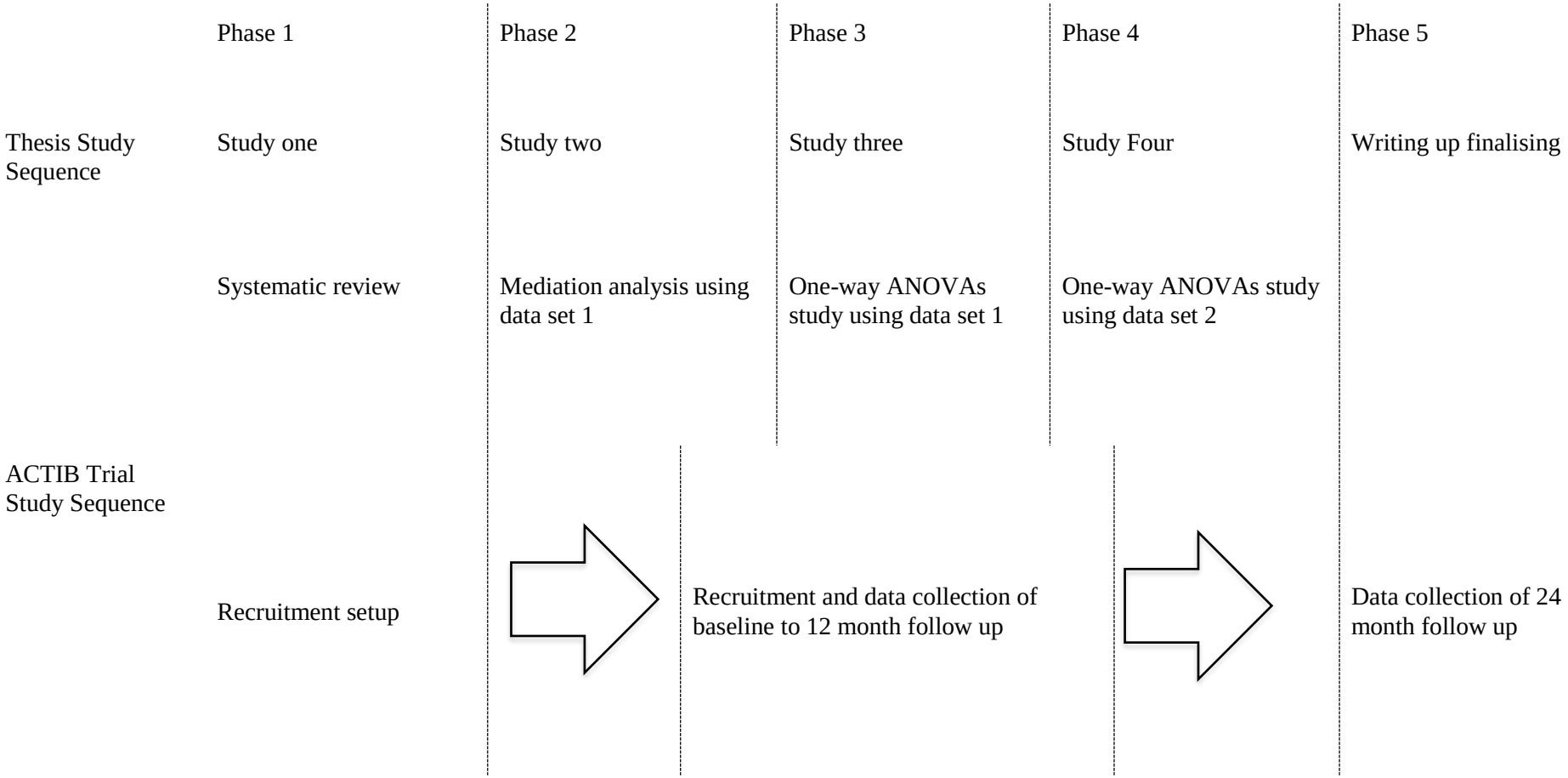

Figure 2.3: Overview of thesis study sequence

2.5 Chapter Summary

This chapter provided an overview of the two RCTs that produced the data used in this thesis. Both RCTs assessed the efficacy CBT-based interventions in improving symptom severity and work and social adjustment in irritable bowel syndrome. There were distinctions between data set 1 and data set 2 in trial design, the samples recruited and the interventions delivered. The sample in data set 1 was smaller (n=148) than data set 2 (n=557). Individuals recruited in data set 2 had refractory IBS, whereas this was not an inclusion requirement in dataset 1. Furthermore participants in dataset 2 met the Rome III criteria for IBS diagnosis, whereas participants in data set 1 met the earlier iteration of the Rome I criteria. The key differences in the interventions delivered were that in data set 1, CBT was delivered face to face by a trained nurse but in data set 2, all therapy delivered was over the phone (in TCBT and WBCBT). The therapy in data set 2 was delivered by highly experienced CBT therapists and clinicians specialising in the delivery of CBT to LTC/MUS patient populations. The models of CBT used in both studies differed slightly. In data set 1, the protocol used a three system's CBT model of IBS whereas in data set 2 the intervention followed a more four-factor approach (appendix F).

All data collection was complete for data set 1, however data set 2 data collection is still in progress, allowing only baseline data available to use for analysis in the present thesis. This chapter outlined the aims and methods of four studies conducted using both data sets and a systematic review of the existing literature. The objectives of these studies were (1) to assess whether cognitive and behavioural factors were mediators of treatment effect on the outcomes of symptom severity and work and social adjustment/quality of life, and (2) to identify cognitive and behavioural factors associated with IBS bowel pattern subtypes.

3. Importance of Mediation Analysis

3.1 Chapter Overview

The introduction (chapter one) provided some background to the efficacy of psychological treatments in improving symptom severity and quality of life in irritable bowel syndrome (IBS). The concept of treatment mechanisms was introduced with the assertion that establishing how psychological therapies exert positive effects on outcomes is important for the modification and enhancement of future treatments. Chapter two detailed (1) a systematic review of mediation studies conducted in the context of IBS (study one) (2) a mediation analysis assessing simple and sequential mediation models including cognitive, behavioural and affective process variables as mediators (study two).

This chapter explores the concept of treatment mechanisms further, presenting the statistical approach of mediation analysis to provide a methodological background for studies one and two. The basic principles of mediation analysis, an overview of different potential ways to conduct the analysis and the advantages and limitations of such approaches are considered. The utility of mediation analysis in furthering the theoretical understanding and clinical benefit of psychological treatments is presented with examples from studies in IBS.

3.2 Published Paper

This chapter is published in the following article:

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Establishing how psychological therapies work: the importance of mediation analysis.

Abstract

This editorial reviews the literature regarding psychological studies that are designed to address the question of not just whether, psychological interventions effect change, but how. The practicalities and implications of assessing mechanisms of treatments are considered with examples from the fields of Cognitive Behavioural Therapy (CBT) and Mindfulness. The potential for elucidating theoretical mechanisms, developing new theoretical models and modifying treatment approaches are described. In addition an overview of different types of statistical methods available to researchers for assessing mediation is given. Structural Equation Modelling (SEM) is a recommended approach. The review concludes with a summary of optimum study conditions adopted by researchers for establishing mediating effects.

What is mediation?

Psychological studies generally focus on measuring whether an intervention works or not through the use of specific patient reported outcome measures (Neale & Strang, 2015). It is less often that researchers investigate *how* interventions exert their effects on an outcome. The investigation into ‘‘how’’ is an investigation into mediation, which seeks to understand the mechanisms in process to produce outcomes.

When the effect of one variable, often an intervention, has its effect on an outcome through change in a third variable, mediation is said to occur. This third variable is called the mediator. Mediators of treatment effects are sometimes described as the treatment effect mechanisms.

Investigating mediation is important both for the advancement of psychological theory and refinement of clinical practice. The study of psychological mediators can allow us to capitalise upon key processes involved in generating positive outcomes. This editorial aims at providing a basic understanding of mediation, giving a sense of its scope, and to illustrate that despite this sort of analysis potentially requiring some specialist knowledge, it is critical to advance understanding of psychological therapies. Critical evaluation of current research into mediational processes from psychological intervention studies are provided, to demonstrate the importance and value of the study of mediation as well as potential limitations that may arise in such analysis.

Study design considerations

Randomised Controlled Trials (RCTs) are considered to be the gold standard of assessing therapeutic change (Evans, 2003) and they are also the optimum study design for establishing mediation. Randomisation allows researchers to assume that there are no variables confounding the relationship between intervention and mediator, or between intervention and outcome. However, this design does not preclude the possibility that there may be unmeasured variables confounding the relationship between mediator and outcome, as generally the mediator is not randomised (MacKinnon & Pirlott, 2015). Confounders are discussed further in the section below. Ideally the design of RCTs would incorporate mediation analysis as an integral part of the design phase. As such this would involve considered inclusion of mechanism measures as well as outcome measures, with stipulation of how many times and at what time points these are assessed. The variables to be included in mediation analysis should be informed by theory and/or empirical studies, to avoid ‘‘fishing’’ which may

cloud theoretical understanding (Johansson & Høglend, 2007).

How is Mediation Established?

The literature regarding mediation in psychology is growing, as evidenced by the increasing number of citations of Baron & Kenny's seminal paper published in 1986 (Baron & Kenny, 1986). The Baron and Kenny article presents mediation in a three variable path model. The three variables are:

- R= randomisation
- M= mediator
- Y= outcome variable (an appropriate measure of therapeutic change)

The model is demonstrated in Figure 1, which illustrates the path after R on Y ''(path c)'', representing the overall treatment effect of R on Y. Panel B includes a depiction of both the direct effect of R on Y through path c' and also the indirect effect of R on Y through M involving paths a and b. The potential unmeasured confounding variables – as mentioned in the previous section – are represented by U.

Baron and Kenny's methodology asserts that a series of regressions be conducted to establish the statistical significance of relationships between the variables in the different paths. The series of regressions seeks to infer the mechanistic process of M by ascertaining whether: (1) in a regression of Y on R (path c), the effect of the intervention variable is statistically significant (2) in a regression of M on the R (path a), the effect of the intervention variable is statistically significant (3) in a regression of Y on R (path c'), and M (path b) the effect of the mediator is statistically significant (4) in the regression in (3), the intervention effect is no longer statistically significant when controlling for the mediator.

Baron and Kenny assert that the strongest evidence for mediation is when the effect of the intervention in regression (3) is reduced to zero, which is generally referred to as ''full mediation''. If the effect of the mediator and intervention are significant in (3), or if the effect of the mediator is significant and the effect of the intervention is not zero, but is lessened when controlling for the mediator, this is generally referred to as partial mediation, and the assumption is that there are other mediators influencing the effect of the intervention on the outcome that haven't been included. This method is sometimes referred to as the causal steps approach to mediation (MacKinnon et al., 2002, 2007).

Although this method of testing mediation is now widespread in the literature, there are limitations associated with the method that have been discussed elsewhere (Emsley et al., 2010; Kazdin, 2007; MacKinnon et al., 2002; Zhao et al., 2010).

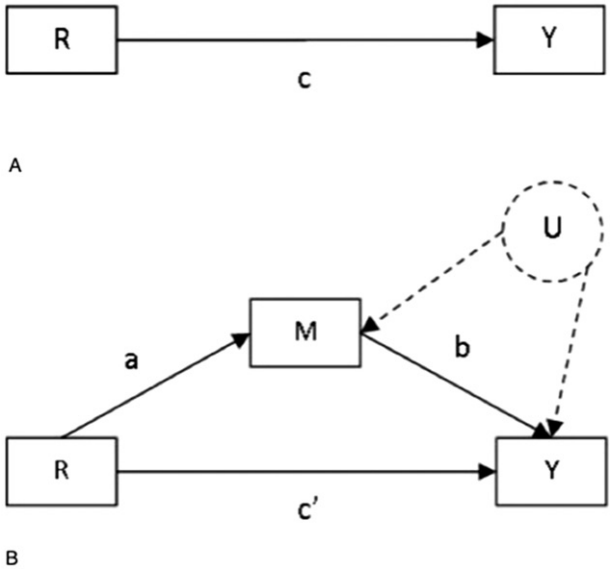

Figure 1: Simple mediation model. Panel A depicts R →Y model and panel B depicts R → M →Y mediation model.

One issue with the method is the requirement for a significant intervention effect as stated in (1). Along with others (Emsley et al., 2010; MacKinnon, 2008), we do not agree that mediation should only be investigated when there is a significant intervention effect. It may be even more important to study mediation where this is not the case; in order to determine if the intervention does not have the desired effect on the mediator, the mediator does not have an effect on the outcome, or if there is evidence of suppression (MacKinnon et al., 2000; MacKinnon, 2008). Suppression occurs when the indirect and direct effects oppose one another.

Another difficulty with the causal steps method is that it does not directly quantify the indirect effect through the mediator. Instead it relies on a number of hypothesis tests to make inferences about mediation. In addition, this method has been shown to have low power to detect mediated effects. In other words, researchers using this method may miss effects even when they are present (Hayes, 2009; MacKinnon et al., 2002, 2007; Preacher & Hayes, 2008). Finally, Baron & Kenny did not address the possibility of

biased results due to unmeasured confounding variables i.e. variables which may influence both the mediator and the outcome. The omission of such confounding variables could bias the results of mediation analysis (Emsley et al., 2010; MacKinnon, 2008). This issue was presented in the earlier and less referenced paper by Judd & Kenny (1981), and can be at least partially dealt with by measuring potential confounders and including them in the regression models.

Another issue that was brought to the fore in both the Baron & Kenny and Judd & Kenny papers (Baron & Kenny, 1986; Judd & Kenny, 1981) was measurement error in variables, which could also lead to biased effect estimates. Measurement error is likely to be of particular concern in psychology and psychiatry, where we are often interested in unobservable or latent traits. Structural Equation Modelling (SEM) allows modelling of relationships between underlying latent trait variables, each quantified by several scale items or measures. For example maladaptive cognitions may be measured using a questionnaire, which includes several items that could be indicative of such cognitions (‘‘I am no good’’, ‘‘they probably think I can’t do this’’). In this example the latent trait is maladaptive cognitions. By utilising multiple items or measures and modelling latent variables, SEM account for measurement error and elucidate relationships between latent traits (Bollen & Pearl, 2013; MacKinnon, 2008). SEM utilising only observed variables is referred to as Path Analysis Models (MacKinnon, 2008).

Like the use of Baron & Kenny’s Framework, the use of SEM for investigating mediation has also been criticised. However, it has been noted that rather than an issue with the method itself (Bollen & Pearl, 2013; Emsley et al., 2010; MacKinnon, 2008), this is more to do with improper or non- specification of theoretical models and disregarding assumptions in interpreting results (Bollen & Pearl, 2013; Emsley et al., 2010; MacKinnon, 2008). An important advantage to the SEM approach to mediation is that SEM can simultaneously model multiple outcomes/regressions as well as multiple mediators (MacKinnon, 2008). To summarise, two main benefits of SEM are: the ability to allow for measurement error (Little et al., 2007), and the ability to investigate more complex models of mediation.

Mediation in psychological research

As already identified, one benefit of mediation research in psychological studies is the potential for therapeutic approaches to be enhanced. By pinpointing mediating mechanisms, therapeutic processes may be refined to focus on specific aspects of therapy that lead to improvements in outcomes, with the possibility of discarding

aspects that are less relevant (Kazdin, 2007). This could lead to more efficient and effective delivery of therapy. Uncovering mechanistic processes can also be useful for development and enhancement of treatments that can be used transdiagnostically across different conditions, tackling a range of outcomes simultaneously. An advantage to the development of transdiagnostic treatments is to potentially streamline the approach to treatment of individuals with multiple symptoms or comorbidities (Clark & Taylor, 2009; Newby et al., 2015).

Investigations of the mechanistic processes of psychotherapies are increasing, although currently the literature remains limited. Psychotherapies that have been more widely subjected to mediation analysis include cognitive behavioural therapy (CBT) (Maric et al., 2013; Odondi et al., 2013; Turner et al., 2007; Whisman, 1993) and mindfulness based therapies (MBTs) (Bränström et al., 2010; Coffey & Hartman, 2008; Sears & Kraus, 2009).

Investigating proposed theoretical mechanisms

One practical use of mediation analysis is to evaluate theoretically implicated process variables. This can advance both theory and therapeutic practices. Given that it is now widely used transdiagnostically, CBT is an example of a therapy where mechanism evaluation is particularly import- ant. CBT is designed to alter negative patterns of thinking and behaving that are considered to cause and/or maintain symptoms and disability across a wide variety of conditions. The proposed mechanisms of change at a broad level are cognitions and behaviours. Investigation into whether these processes are indeed responsible for improved outcomes as a result of CBT have been conducted in the context of chronic pain (Turner et al., 2007), panic disorder (Hofmann et al., 2007), chronic fatigue syndrome (Chalder et al., 2015; Moss- Morris et al., 2005; Stahl et al., 2014) and irritable bowel syndrome (IBS) (Lackner et al., 2007; Miklowitz & Scott, 2009; Reme et al., 2011) amongst other disorders (Hofmann et al., 2012).

Specific CBT models have been developed to explain certain conditions such as depression (Beck et al., 1987), medically unexplained symptoms (Deary et al., 2007), and IBS (Toner et al., 2000). Such models provide a basis for empirical investigation, which in turn allow the validation and development of the models. In the context of IBS for example, the CBT model postulates that reduction in symptom severity and impact on life is due to treatment-induced changes in conceptualisation of bowel symptoms (Toner et al., 2000). This reconceptualization should involve changes in beliefs about IBS being an uncontrollable medical problem and increases in

behavioural strategies that can be employed in the face of symptoms. One particular study examining cognitive and behavioural mechanisms in IBS found evidence supportive of this (Reme et al., 2011). The mediator variables tested included the Cognitive Scale for Functional Bowel Disorders (CS-FBD) (Toner et al., 1998) and the Behavioural Responses Questionnaire for IBS (IBS-BRQ) (Reme et al., 2010). The CS-FBD includes items relating to specific beliefs about functional bowel disorders such as ‘‘It is embarrassing to keep going to the toilet’’. The IBS-BRQ includes specific items for behaviour implicated in IBS such as ‘‘I avoid exercise when I have stomach pains’’.

The analysis found that change in both cognitions and behaviours mediated the reduction in symptom severity and impact on life. SEM was used to apply a sequential mediator model indicating that behaviours changed prior to cognitions (Reme et al., 2011). In this study, the mediator variables included in the analysis were taken from the same time point as the outcome variables. Mediation implies a causal process, where treatment is applied first, followed by a change in the mediator, which is then followed in turn by a change in the outcome. Studies with mediator and outcome measures taken at the same time may provide weaker evidence for treatment mechanisms as the implied temporal ordering has not been incorporated in the study design. The rationale in this case was that there was no significant further change in mediator variables assessed at later time points and therefore it made little difference to use scores from later time points in analysis. Nevertheless, it is more theoretically sound to design studies that respect this implied temporal ordering. Therefore, studies should aim at including mediators measured at time points prior to the outcome variable. This is given further consideration later.

Where the focus of interventions differ within the same school of psychotherapy, mediation can be used to clarify the extent to which different processes produce change in outcomes. For example, within CBT as applied to IBS, different researchers postulate the importance of different mechanistic processes, namely a change in cognitions and/or behaviour versus a reduction in distress/anxiety. To date, findings supporting one key process over the other have been inconsistent. This is demonstrated by the differing results in two particular mediation studies investigating CBT for IBS, conducted by Lackner et al. (2007) and Jones et al. (2011). Both studies investigated the potential mediating roles of psychological distress on outcome after CBT for IBS, with conflicting findings. There were, however, some distinct limitations within both studies and also arising from the comparison between them. First of all, both studies

used different measures of psychological distress: Jones et al., used the Hospital Anxiety and Depression Scale measure of anxiety and depression (Snaith, 2003) and Lackner et al., used the Brief Symptom Inventory measure of psychological distress (Derogatis & Spencer, 1993). Whilst Jones et al. provided a clear mediation model informed by theory, Lackner et al., assessed a model of mediation that did not appear to be informed by theory. The path model of Jones et al., arranged variables into a sequence informed by an interpretation of the Biopsychosocial model (Drossman, 1998), in which CBT alters mood (anxiety and depression) positively, which then reduces bowel symptoms. In contrast, Lackner et al., assessed a complex path model with no clear theoretically informed structure, in which there were three direct paths from CBT to all three outcomes (quality of life, global symptom improvement and distress) as well as multiple indirect paths between the different outcome measures.

Jones et al. found that anxiety and to a lesser extent depression had a mediating effect, whereby decreases in both led to a reduction in symptom severity. On the other hand, Lackner et al. did not find psychological distress to be a significant mediator. They instead found that CBT had a direct effect on symptom severity independent of distress. Lackner et al.'s findings are supported by more recent mediation analysis, which also found that distress was not a significant mediator (Chilcot & Moss-Morris, 2013). This study included a measure of cognitions and behaviours, finding that cognitions significantly mediated the effect of treatment on symptom severity. This strengthens support for a cognitive behavioural model for IBS in which change in outcome is mediated by cognitions rather than distress.

The example of the Jones and Lackner studies illustrates a number of limitations within the current mediation literature: (a) Results will be dependent on which mediation variables are entered in the analysis. It is important for mediation studies to be fully informed by theory to allow for examination of all possible mediators as dictated by the theoretical model. (b) Different measures may be utilised to measure concepts that are the same or similar, which can limit interpretation across studies e.g. a measure of anxiety vs. a measure of psychological distress. (c) Different approaches to mediation analysis may affect findings. This will be considered later in the article and (d) It may be that there is a longer mediation chain that involves more than one mediator variable in the causal path where one mediator may serve to mediate the effects of another mediator (Taylor et al., 2008). In this example, this would occur where change in cognitions mediates change in psychological distress, which then accounts for change in the outcome of symptom severity.

Developing theory

The previous section described the use of mediation studies to examine processes guided by psychological theory. Here we consider how mediation analysis can provide opportunities to build theory, which we refer to as ‘‘back translation’’. Mindfulness research provides an opportunity in which to consider the application of back translation. The provision of MBT is growing across different clinical populations, yet the theoretical underpinnings of such practice remains scarce. An initial theory, by which mindfulness was proposed to exert clinical effects, was published in 2006 (Shapiro et al., 2006). The theory asserted that four variables identified as changes in self-regulation, values, flexibility (cognitive, emotional and behavioural) and exposure to internal processes, may act as mechanisms responsible for outcomes such as reduction in symptoms or distress. These processes were asserted to be achieved through increased ‘‘re-perceiving’’ and ‘‘de-centering’’. These pertain to the ability to maintain objectivity towards experience.

This theory was tested by Carmody et al. (2009), using the causal steps approach to mediation. There were some methodological issues associated with this study that should be considered. First, participants were not randomly allocated to different groups so analysis was conducted without the use of a comparator control group. Secondly, some of the measures lacked established reliability and validity. Some of these measures were then altered further before being entered into the mediation analysis, as the authors created a composite unitary measure of mindfulness, re-perceiving and de-centering; variables that were identified as distinct in the theoretical model described by Shapiro et al. (2006). The analysis utilised the Baron & Kenny causal steps approach, with the limitations detailed earlier in this paper. Finally, the authors did not include measures assessed at differing time points further reducing causal inference.

The results of the analysis found that the effects of composite mindfulness/re-perceiving on psychological symptoms, were found to be partially mediated by two of the four processes identified in the model: Cognitive, emotional and behavioural flexibility and values clarification. Rather than providing conclusive evidence for the hypotheses proposed by Shapiro et al. the results served as a basis upon which to focus further investigations, also highlighting the possibility that there may be other mediating processes unaccounted for in the model.

Both theory and empirical study have been a basis for further investigations into

important processes of mindful- ness, such as cognitive and behavioural flexibility (Baer, 2010; Heeren et al., 2009; Hölzel et al., 2011; Kuyken et al., 2010). Elements closely associated with mindfulness and nested within the model, such as self-compassion (Baer et al., 2012; Hayes et al., 2004; McCracken & Velleman, 2010; Neff, 2003; Petrocchi et al., 2014), have continued to attract research focused on the examination of mechanisms of MBTs (Baer, 2010; Hölzel et al., 2011; Kuyken et al., 2010). Most recently, a systematic review of empirical studies investigating proposed mechanisms of MBTs on a range of clinical outcomes identified some key processes (Chiesa et al., 2014). These included cognitive reactivity, experiential avoidance, emotion regulation and self-compassion. The accrual of empirical evidence of such processes will continue to provide cumulative insights informing more comprehensive and developed models (Bullock et al., 2010).

Shared mechanisms in psychotherapy

Another reason for investigating mediation in the context of psychotherapy is to elucidate mechanisms that are shared across different psychotherapeutic practices. There is an increasing shift towards transdiagnostic conceptualisation of conditions and treatment approaches (Newby et al., 2015), which is beyond the scope of this article. Nevertheless, it is clear that increasing discovery of efficacious mechanistic processes across treatment approaches and diagnoses, could allow for more unified treatments that are effective for a wide range of outcomes.

In a systematic review of psychosocial treatments for bipolar disorder, common mechanisms across treatments were identified. These included enhancement of interpersonal functioning and teaching self-monitoring to allow early self- intervention during relapses (Miklowitz & Scott, 2009). Such processes have also been implicated in interpersonal therapy (IPT) (Lipsitz & Markowitz, 2013) and can be seen to be present in other therapies such as CBT (Livesley, 2007; Steever, 1999), MBT (Epstein et al., 2008) and counselling (Howey & Ormrod, 2002). It was particularly noteworthy that effective therapies shared a number of common characteristics with regards to how the model of therapy was shared with the patient, how the therapy was delivered and the structuring of treatment (Miklowitz & Scott, 2009). Shared characteristics included individualized formulation (tailoring approaches to meet the patients' needs and understanding), openly sharing the therapy model with the patient, a clear rationale for techniques used that were logical to the patient, an emphasis on psychoeducation and skill development, attributing change to the patient's efforts and the encouragement of the continued use of illness management techniques for the

patient post therapy.

Other disease specific systematic reviews conducted have further demonstrated the existence of shared mechanisms across different therapeutic approaches. In a recent review of mechanisms in psychosocial interventions for cancer, self- efficacy in the use of coping strategies and changes in cognitions mediated treatment outcomes in CBT, psycho- education and relaxation training (Stanton et al., 2013). However, it should be noted that the outcomes across studies varied. The outcomes were broadly classified into the following domains: psychosocial adjustment, self-reported physical health indicators and biological health indicators. Future reviews establishing mediation across the same or similar outcomes would provide an opportunity to test the hypothesis that the effects of mediators on such outcomes are the same across therapies.

Scope of mediation analysis

Mediation can be a complex process to conceptualise theoretically as well as to approach statistically. Some particular areas for researchers to focus on are discussed below.

Different approaches to mediation

The ‘‘product of coefficients’’ approach (MacKinnon, 2001; MacKinnon & Dwyer, 1993) is an extension of the Baron & Kenny causal steps approach, which can be applied using the SEM framework. This approach is preferred (Hayes, 2009; MacKinnon et al., 2007) over causal steps. Product of coefficients calculates the indirect (mediated) effect by multiplying the intervention regression coefficient in path a, by the mediation regression coefficient in path b (Figure 1).

Temporal precedence

The design of RCTs can allow for the theoretically implied temporal ordering of the mediation model, and ascertain the effects of an intervention (R) that occurs prior to the mediator (M) and outcome (Y) (Figure 1). This may not be as readily possible in observational studies, in part due to the potential for more sources of confounding. However, simply studying mediation in the context of an RCT is not sufficient to establish causal relationships (Emsley et al., 2010, MacKinnon, 2008; VanderWeele, 2015). One helpful approach to gaining understanding of mediational processes is to explore the timeline of mediator and outcome change (Cole &

Maxwell, 2003). Assessing both mediator and outcome measures before, during and after treatment, with assessment at multiple time points is ideal and can provide information about optimal measurement timelines for future studies.

Moderation

The intensity of mediated effects could be dependent on other variables called moderators (MacKinnon, 2008). Moderators are variables that alter the form or strength of the relationship between an independent variable and a dependent variable i.e. R and Y. In other words, when there is moderation, the effect of R on Y varies by a third variable, the moderator X, Moderation is explored in models using interaction terms, so in this case, we would explore the effect of an R by X interaction in a regression model for Y. A moderator may be a variable that is not manipulated such as gender or age. For example it is possible that CBT for depression is more or less effective for different age groups (Jayasekara et al., 2015) as age may change the efficacy of CBT. Moderators may also be experimentally manipulated. For example, participants may be randomly assigned to the same treatment with different levels of therapist warmth and empathy, to ascertain whether therapist warmth and empathy moderates outcome (Harper Romeo et al., 2014). Moderation is important to assess the generalizability of research findings. It is also useful in psychological research for identifying participant subgroups for whom treatment may be more or less effective.

Moderated mediation

Moderated mediation occurs when the strength of an indirect effect (mediation) depends on another variable (moderator) (MacKinnon et al., 2007). As such the meditational mechanism differs for different subgroups (e.g. age, gender, levels of distress). For example CBT (R) may reduce symptom severity in IBS (Y) through a change in cognitions (M). Age (X) may moderate the change in cognitions, for example, older participants may experience less change in cognitions. Discovering such a relationship would highlight the need to investigate why age may act as a barrier to cognitive change, resulting in empirical testing of possible solutions. Such analysis into these underlying processes can provide greater potential for tailoring treatments to subsets of patients within heterogeneous populations (Bullock et al., 2010).

Summary

The full complexity of investigating mediation, moderation and moderated mediation

is beyond the scope of this article, however some possible reasons for differing findings across mediation studies within the same area have been put forward. These include the use of different statistical approaches to mediation, different measurements of similar variables, inclusion or non-inclusion of variables as dictated (or not) by theoretical models and the inclusion or non-inclusion of confounding variables in analysis. Furthermore, considering the intuitive and comparatively simplistic nature of the causal steps approach, it also makes sense that this has been the predominant method of establishing whether mediation occurs. This being so, it would be useful if researchers undertaking mediation analysis would adopt more sophisticated methods where appropriate (Hayes, 2009; MacKinnon et al., 2002, 2007; Zhao et al., 2010). The widely prevalent use of the causal steps approach to mediation has resulted in a number of misconceptions, including the idea that a statistically significant effect of an intervention is necessary before it is advisable to test for mediation; and that a decrease in variance accounted for in the R – Y relationship after inclusion of a mediator is sufficient to conclude there is mediation (Stanton et al., 2013). Happily, researchers interested in mediation analysis can now refer to a burgeoning literature on best practices in the modern study of mediation (Dunn et al., 2013; Hayes, 2009; MacKinnon, 2008; VanderWeele, 2015).

In the context of psychological studies, the study of mediation is critical if we are to understand how therapies exert their effects, test psychological models of therapeutic mechanisms, and most importantly, improve outcomes for our patients. The more mediation studies that are conducted in a more rigorous fashion, the more insight can be gathered into therapeutic mechanisms, which may be transdiagnostic, such as in the case of CBT (Murphy et al., 2009; Newby et al., 2015). Future randomised studies of psychological therapies should therefore include mediation analysis in their design wherever possible, with the inclusion of potential mediator measures informed by theory. Measurements should be taken early and at multiple time points, with concomitant measurement of potential confounders in order to allow for detailed and robust assessments of mediational processes. A recent innovation launched by the UK National Institute of Health Research (NIHR) has provided opportunities for funding specifically for Efficacy and Mechanisms Evaluation (EME) studies (Dunn et al., 2013; Walley & Thakker, 2008), with mediation studies being one aspect of the remit. This, and the growing interest in, and literature focused on mediation are positive steps that have and will continue to increase the use of robust methodological approaches for studying mediation and moderation in psychological research (Freeman et al., 2015).

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4. Systematic Review of Mediators in Psychological Therapies for IBS

4.1 Chapter Overview

Previous chapters have identified the importance in assessing mechanisms by which psychological therapies may have an effect on outcomes. To fulfil objective one of this thesis, a systematic review was conducted. The aim of this review was to identify psychological factors that mediated the effect of psychological interventions in IBS on the outcomes of symptom severity and or/quality of life. It was hypothesised that cognitions, behaviours and anxiety would significantly mediate treatment effect, in line with cognitive behavioural models of IBS (Kennedy et al., 2005; Craske & Barlow, 2006; Moss-Morris et al., 2010). The results of the review are important for informing the mediation study (chapter five) in terms of the design of the analysis and forming hypotheses.

4.2 Published Paper

This chapter is published in the following article:

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Article Title: The journey between brain and gut: A systematic review of psychological mechanisms of treatment effect in irritable bowel syndrome

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The journey between brain and gut: A systematic review of psychological mechanisms of treatment effect in irritable bowel syndrome

Purpose: Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by abdominal pain and altered bowel habits. It is estimated to affect 10–22% of the UK population. The use of psychological interventions in IBS is increasingly empirically supported, but little is known about the mechanism of psychological treatment approaches. The present systematic review aimed to investigate the mechanisms of psychological treatment approaches applied to IBS.

Methods: The systematic review included studies conducting mediation analysis in the context of psychological interventions for IBS, focusing on the outcomes of symptom severity and/or quality of life (QoL).

Results: Nine studies in total were included in the review. Eight of the studies assessed mediation in the context of cognitive behavioural-based interventions, and one study assessed mediation in a mindfulness-based stress reduction intervention. Results indicate that change in illness-specific cognitions is a key process by which psychological treatments may have an effect on the outcomes of symptom severity and QoL. Furthermore, results suggest that whilst GI-specific anxiety may also be a key mechanism of treatment effect, it would appear that general or state anxiety is not. Although less commonly included in mediation analysis, illness-specific behaviours may also have a mediating role.

Conclusions: A mediational model amalgamating the results of studies is proposed to illustrate the findings of the review. The model depicts the process by which psychotherapy changes illness-specific cognitions, behaviours, and anxiety to achieve reduction in symptom severity.

Introduction

Irritable bowel syndrome: definition, aetiology, and prevalence

Irritable bowel syndrome (IBS) is a chronic disorder that usually involves periods of remittance in between flare-ups that may vary in severity. The diagnosis of IBS is based on the absence of any other physiological markers that explain the experience of symptoms. For this reason, many people with a diagnosis of IBS may have undergone several investigative procedures prior to diagnosis. The prevalence of IBS in the general population is estimated to be 10.5% (Wilson, Roberts, Roalfe, Bridge, & Singh, 2004). This varies across ages and gender, with women aged between 30 and 39 being twice as likely to experience it than men of the same age range (Dalrymple & Bullock, 2008). IBS is associated with impaired quality of life (QoL) and distress (Athanasakos & Emmanuel, 2013; Wu, 2012) as well as high rates of comorbidity of anxiety (Fond *et al.*, 2014).

The ROME criteria were developed to classify functional gastrointestinal disorders that were not otherwise explained by structural or tissue abnormalities. The most recent ROME IV criteria asserts that the prevalent symptom of IBS is abdominal pain, which must be associated with changes in bowel movements or stool consistency (Drossman, 2016). The criteria identify four bowel subtypes: constipation predominant (IBS-C), diarrhoea predominant (IBS-D), alternating bowel pattern (IBS-A), and unclassified (IBS-U). These subtypes are categorized based on the proportion of symptomatic stools that are loose/watery or hard/lumpy.

Brain–gut axis

Although the cause of IBS remains unclear, increasing credence is given to the biopsychosocial aetiological model of IBS (Engel, 1981). This proposes that symptoms occur due to an interaction between biological, psychological, and social mechanisms (Mayer, Labus, Tillisch, Cole, & Baldi, 2015; Quinton & Keefer, 2014; Van Oudenhove *et al.*, 2016). A physiological system by which this interaction may occur is referred to as the ‘brain–gut axis’ (BGA; Jones, Dilley, Drossman, & Crowell, 2006). The BGA is a bidirectional communication between the enteric nervous system (ENS) located in the walls of the gastrointestinal (GI)

tract, and the autonomic and central nervous systems (Fichna & Storr, 2012). The mechanism of communication involves the autonomic stress response and the endocrine, neuroimmune, and neural pathways (Wu, 2012; Kennedy *et al.*, 2012) utilizing the hypothalamic–pituitary–adrenal axis (HPA axis). A recent review comprehensively explains how the BGA underpins the psychological, social, and physiological interactions to contribute to the experience of symptoms in functional bowel disorders (Van Oudenhove *et al.*, 2016). The BGA is therefore the proposed physiological mechanism by which psychological factors can exert effect on physical outcomes such as symptom severity (Van Tilburg, Palsson, & Whitehead, 2013).

Psychological treatments in IBS

It is well established that psychological factors affect both QoL and symptom severity in IBS (Van Tilburg *et al.*, 2013), and psychological treatments have been developed over the years to target such factors. Meta-analyses and systematic reviews have established the efficacy of psychological treatments in reducing symptom severity in IBS (Ford, Talley, Schoenfeld, Quigley, & Moayyedi, 2009; Kennedy *et al.*, 2012; Lackner, Mesmer, Morley, Dowzer, & Hamilton, 2004; Li, Xiong, Zhang, Yu, & Chen, 2014). The most commonly utilized psychological treatments in IBS are considered below in terms of the underlying theoretical model, mechanisms, and empirical support.

Cognitive behavioural therapy (CBT)

To date, the majority of psychological interventions conducted in IBS are CBT-based, with strong empirical support demonstrating its efficacy in reducing symptom severity and enhancing QoL/impact on life (Ford *et al.*, 2009, 2014; Li *et al.*, 2014). This being said, there is not one agreed CBT protocol for IBS and different studies use different models and treatment techniques (Henrich *et al.*, 2015).

Some protocols may put more emphasis on targeting general or state anxiety, as opposed to gastrointestinal-specific anxiety (GSA; Blanchard *et al.*, 2007; Lackner *et al.*, 2007). Protocols, focusing on GSA, tend to more heavily utilize exposure-based techniques (Craske *et al.*, 2011; Hunt, Moshier, & Milonova, 2009; Ljótsson *et al.*, 2010). It has also become common for CBT protocols to include mindfulness (Ljótsson *et al.*, 2010; Wolitzky-Taylor, Craske, Labus,

Mayer, & Naliboff, 2012). Other protocols follow a three-systems model, specifically focusing on the change of illness-related cognitions and behaviours (Kennedy *et al.*, 2005, 2006), as opposed to the targeting of thoughts and behaviours more commonly related to general anxiety. Although there may be shared mechanisms of change across protocol approaches, the way in which treatment works may differ between studies depending on the model and interventions used.

Hypnotherapy

Hypnotherapy (HT) as applied to IBS is called 'gut-directed' or 'gut-focused' HT. The process involves the use of hypnotic techniques that are designed to relax the automatic reaction to symptoms and allows individuals more control in their cognitive and physical response to them (Gonsalkorale, Toner, & Whorwell, 2004). Sessions consist of induction of a hypnotic state and hypnotic suggestions to reduce threat perception of symptoms. Evidence suggests that this approach is effective in improving both physical symptoms of IBS and enhancing QoL (Miller *et al.*, 2015; Wilson, Maddison, Roberts, Greenfield, & Singh, 2006).

There has been substantial interest in the mechanisms of HT in IBS (Simrén, 2006; Spiller *et al.*, 2007; Tan, Hammond, & Gurrala, 2005). One of the key mechanisms consistently implicated in the literature seems to be the role of cognitions. One particular study found that after HT, IBS improvement was associated with a reduction in IBS-related cognitions (Gonsalkorale *et al.*, 2004). The authors suggested that the hypnotherapeutic approach used could be regarded as a form of cognitive restructuring as it involved techniques to increase individuals' perceived control over symptoms.

Psychodynamic psychotherapy

Psychodynamic psychotherapy for IBS aims to reduce symptoms through enhancing interpersonal relationships, which are purported to be the underlying source of symptomatic complaints (Guthrie, 2002). This approach is called 'psychodynamic interpersonal therapy' (PIT). Sessions are designed to provide individuals with insight into the link between interpersonal difficulties and symptoms, and between emotions and bowel symptoms. A limited number of studies have assessed the efficacy

of PIT for IBS with some support for its efficacy in reducing symptom severity (Creed *et al.*, 2003; Guthrie, Creed, Dawson, & Tomenson, 1991; Svedlund, Ottosson, Sjödin, & Dotevall, 1983).

There is not an established model by which PIT is proposed to improve IBS symptoms; however, Hyphantis, Guthrie, Tomenson, and Creed (2009) hypothesized that PIT would lead to a reduction in IBS symptoms, by reducing psychological distress associated with interpersonal conflict. This study assessed the mediating effect of psychological distress on interpersonal distress, finding significant mediation. It did not however assess the relationship between treatment, these processes, and the outcome of symptom severity.

Establishing mechanisms of psychological treatments for IBS

The primary way to elucidate mechanistic processes in psychological research is by conducting mediation analysis (Baron & Kenny, 1986; MacKinnon, 2008; Windgassen, Goldsmith, Moss-Morris, & Chalder, 2016). This allows potential mechanistic variables to be assessed in the context of the proposed pathway between treatment and outcome (Kazdin, 2007). A simplistic model of mediation is illustrated in Figure 1. This demonstrates how a treatment may cause change in an outcome, by first eliciting change in a mediating variable. An early approach to conducting mediation analysis was proposed by Baron and Kenny (Baron & Kenny, 1986), utilizing a series of regressions. Mediation is said to occur where I is shown to no longer influence (or have less of an influence on) O when M is controlled for. This approach is sometimes referred to as the 'Causal Steps' approach to mediation (MacKinnon, Fairchild, & Fritz, 2007; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).

Structural equation modelling (SEM) is another statistical method to assess mediation. SEM is sometimes referred to as 'path analysis' when it is conducted utilizing observed variables (MacKinnon, 2008). SEM can also allow the modelling of relationships between variables utilizing underlying latent traits and allow models to account for measurement error (Bollen & Pearl, 2013; MacKinnon, 2008). An advantage to the SEM/path analysis approach to mediation is that it can model multiple outcomes/regressions simultaneously, which allows for longitudinal modelling of multiple measures of mediators and outcomes. In practical terms, this means that numerous

mediators identified by a theoretical model have their impact on outcome assessed simultaneously.

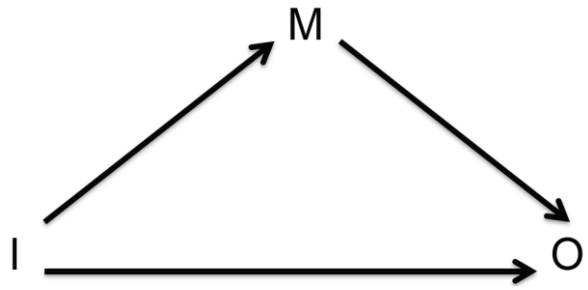

Figure 1: Simplistic Mediation Model: I is the treatment or intervention, M the mediating variable through which I has an effect on O the outcome.

Although the number of studies empirically investigating the efficacy of psychological therapies for IBS has increased, little is known about how psychological treatments work (Murphy, Cooper, Hollon, & Fairburn, 2009). Investigating the key processes involved in creating change in outcome is important to identify components of therapy that are necessary for achieving desired outcomes. It therefore also provides opportunity for treatment modification and enhancement. The present review aimed to systematically assess psychological variables shown to significantly mediate treatment effect on the outcomes of symptom severity and QoL.

Methodology

The systematic review methods adhered to PRISMA guidelines to ensure the standardized reporting of systematic reviews (Moher, Liberati, Tetzlaff, & Altman, 2009).

Literature search

The search was conducted using electronic databases Ovid, PsycInfo, Embase, MEDLINE, PsycArticles, and Global Health. The search was conducted three times in the months April 2014, June 2014, July 2015, and May 2016 (Appendix S1). One additional paper was identified by searching citations of the included papers.

Eligible studies

In accordance with the recommendations of the Centre for Reviews and Dissemination (Tacconelli, 2010), the search strategy was developed using a PICOS format. The acronym refers to (P) population (I) intervention (C) comparator group (O) the outcome or endpoint interested in (S) study design. This shaped the inclusion criteria (Appendix S2). To be included studies had to have conducted mediation analysis on an intervention delivered prospectively. This was to ensure that mediation was designed to test mechanisms of efficacy for delivered interventions rather than to explore potential mechanisms of outcome in the absence of an intervention.

Assessing study bias

The Cochrane Handbook stipulates that systematic reviews should assess a risk of bias in included studies (Higgins & Green, 2008). In this systematic review, two separate tools were used. One was designed to assess the overall quality of randomized controlled trials (RCTs) using the original RCT publication, and the other was developed to assess the quality of mediation analysis. The RCT quality assessment (QA) tool (Appendix S3) used was the Cochrane Guide for QA s (Van Tulder, Furlan, Bombardier, & Bouter, 2003). Only two criteria were not included in the present review. These related to (1) blinding of the participants and (2) blinding of the care provider, which were not practical to use due to the nature of the interventions being studied. Papers were rated as 'yes', 'no', or 'unclear' against each criteria. Papers were scored out of a total of 9. Answers of 'no' or 'unclear' scored 0 and answers 'yes' scored 1. This rating is adherent to the recommendations by Cochrane (Higgins & Green, 2008). The papers were rated by the first author and AS.

Two approaches were used to develop the mediation QA tool (Appendix S4). Items were based on a previously developed tool (Lubans, Foster, & Biddle, 2008). Some items were altered to reflect the aims of the present review. Additional items were added to reflect the range in quality across the studies included in review and against standards stipulated in the mediation literature (MacKinnon, 2008).

The additional items were as follows: (1) Was more than one model fit

criteria reported where path models were used in analysis? (2) Was the mediator variable/s assessed for change? (3) Was temporal precedence accounted for in the analysis? (4) Did the study report confidence intervals of the mediated effect? When the Baron and Kenny framework was used, it was stipulated that confidence intervals should be used for paths *a* and *b*. Where SEM or path analysis was used, confidence intervals for the indirect path/s were stipulated.

The additional criteria are detailed in order of their listing: (1) It is recommended that more than one model fit criteria should be used in SEM because each criteria are affected by different factors (such as sample size, model complexity, and data normality; Hair, Anderson, Tatham, & Black, 1992; McDonald & Ho, 2002). (2) It was deemed important to establish whether the mediator was assessed for change, to ascertain whether the interventions were effective in producing change in proposed mediating variables. (3) Studies were rated on the inclusion of design accommodating temporal precedence as this is an important design consideration to allow inferences regarding causality. (4) Confidence intervals were deemed necessary to indicate the magnitude of the path coefficient.

Papers using Baron and Kenny's Causal Steps approach were scored out of 7, whilst other approaches to measuring mediation were scored out of 8. This was because the item regarding assessment of fit criteria was not relevant to the causal steps approach to mediation.

Quality assessment for mediation was conducted by two of the authors, the first author and the fourth author. The third author was used to rate the quality of one paper to minimize the risk of bias as the fourth author was also an author of this study. Any disparities were discussed with all raters during QA, enabling full agreement on criteria.

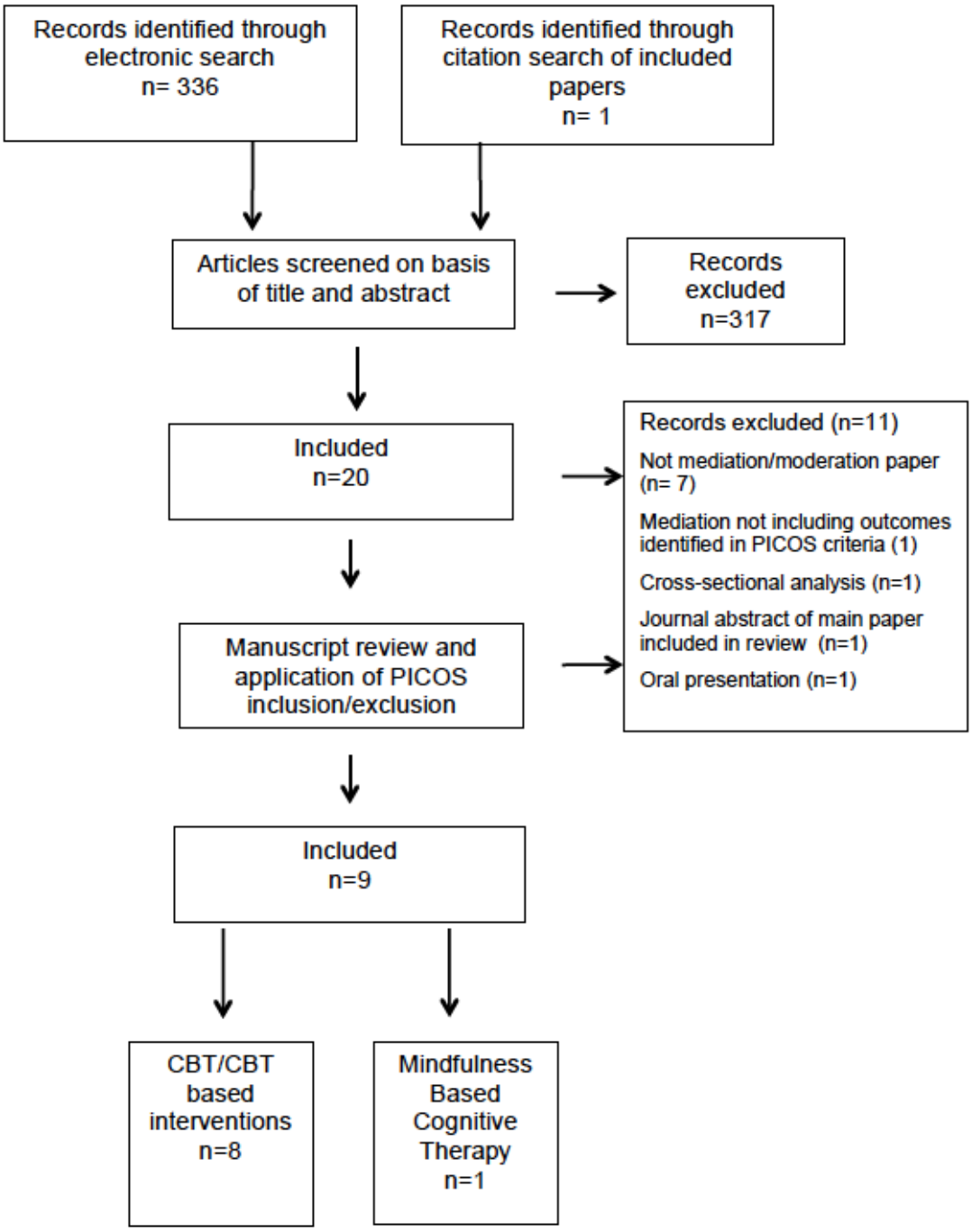

Figure 2. PRISMA flow diagram. The figure details how many papers were excluded at each stage of review.

Results

Three hundred and thirty-seven search results were returned in the initial search. Three hundred and seventeen were excluded after screening titles and abstracts, and removing duplicates (Figure 2). The full text of 20 articles were screened, and nine were left to review (Chilcot & Moss-Morris, 2013; Garland *et al.*, 2012; Hunt *et al.*, 2009; Jones, Koloski, Boyce, & Talley, 2011; Labus *et al.*, 2013; Lackner *et al.*, 2007; Ljótsson *et al.*, 2013; Reme *et al.*, 2011; Wolitzky-Taylor *et al.*, 2012). The most common reasons for exclusion at the full-text screening phase were studies not performing mediation analysis or not conducting an intervention (Figure 2). Two studies that conducted mediation were excluded as they either did not assess mediation of treatment effect on the outcome of symptom severity or QoL (Hyphantis *et al.*, 2009) or they conducted mediation in the absence of an intervention cross-sectionally (Rutter & Rutter, 2002).

Study characteristics

All of the studies included were RCTs. Control groups included wait list control (WL; Hunt *et al.*, 2009; Labus *et al.*, 2013; Lackner *et al.*, 2007), treatment as usual (TAU; Chilcot & Moss-Morris, 2013; Jones *et al.*, 2011), provision of medication (Reme *et al.*, 2011), and alternative psychological or psycho-education interventions (Garland *et al.*, 2012; Jones *et al.*, 2011; Lackner *et al.*, 2007; Ljótsson *et al.*, 2013; Wolitzky-Taylor *et al.*, 2012). Three studies compared the active treatment with two control groups (Jones *et al.*, 2011; Lackner *et al.*, 2007; Wolitzky-Taylor *et al.*, 2012), and the rest utilized a single control group.

Participants were recruited from primary care (Chilcot & Moss-Morris, 2013; Reme *et al.*, 2011), secondary care alone (Labus *et al.*, 2013), a mixture of secondary care and wider community advertising (Garland *et al.*, 2012; Jones *et al.*, 2011; Lackner *et al.*, 2007; Ljótsson *et al.*, 2013; Wolitzky-Taylor *et al.*, 2012) and from online IBS support resources (Hunt *et al.*, 2009). Sample sizes ranged from 54 to 195 (median = 76). The follow-up periods for assessing outcome measures ranged from 3 to 12 months. The range of follow-up periods for outcomes included in the mediation analysis was 6 weeks to 8 months, with only one study

including outcomes up to 8 months in the mediation analysis (Chilcot & Moss-Morris, 2013). A summary of the study characteristics is presented in Table 1.

Quality assessment

RCT quality assessment

Studies ranged in quality from 4 of 12 (Hunt *et al.*, 2009; Labus *et al.*, 2013) to 9 of 12 (Chilcot & Moss-Morris, 2013; Garland *et al.*, 2012). The majority of studies were found to be of moderate quality fulfilling 7 of 12 or above (Appendix S3).

Mediation quality assessment

Three studies met 7 of 8 or 6 of 7 of the QA items (Chilcot & Moss-Morris, 2013; Ljótsson *et al.*, 2013; Wolitzky-Taylor *et al.*, 2012). The majority of the rest were of moderate quality fulfilling 4–5 of 8 of the criteria (Hunt *et al.*, 2009; Lackner *et al.*, 2007; Appendix S4).

Population characteristics

The mean age of participants in each study ranged from 33 to 48. A greater proportion of participants were women (72.5% or greater) as is generally found in IBS populations (Dalrymple & Bullock, 2008). One study chose to recruit only female participants (Garland *et al.*, 2012), with the reasons for this not explained. Classification into types of IBS differed across studies. Only one study used the ROME I (Jones *et al.*, 2011) or III criteria (Ljótsson *et al.*, 2013). The majority of recruited participants conformed to ROME II criteria (Chilcot & Moss-Morris, 2013; Garland *et al.*, 2012; Labus *et al.*, 2013; Lackner *et al.*, 2007; Wolitzky-Taylor *et al.*, 2012). One study relied on GP diagnosis of IBS (Reme *et al.*, 2011) and another on self-reported IBS (Hunt *et al.*, 2009).

The measures of illness severity included the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS; Francis, Morris, & Whorwell, 1997), the Gastrointestinal Symptom Rating Scale modified for IBS (GSRS – IBS; Wiklund *et al.*, 2009), the Bowel Symptom Severity Scale (BSSS; Boyce, Gilchrist, Talley, & Rose, 2000), a composite BSSS measure (Wolitzky-Taylor *et al.*, 2012), a global GI rating using a 20-point rating

scale (Labus *et al.*, 2013), and a physician-rated severity score ranging from symptoms absent to very severe symptoms (Lackner *et al.*, 2007). Samples consisted of participants suffering with moderate-to-severe symptoms. One study did not use classifications of mild-to-severe symptom severity, but instead provided means out of a total possible score of 40 for frequency, distress, and interference of symptoms (Jones *et al.*, 2011).

Therapy models & interventions

Nine of the studies assessed mediation in the context of cognitive behaviourally based interventions. Protocols varied across studies as reflected in Table 2. One study conducted mindfulness-based stress reduction tailored to IBS symptoms (Garland *et al.*, 2012). The method of intervention delivery, duration of sessions, and period of interventions are summarized in Table 1.

Hypothesized pathways

The hypothesized pathways of change are illustrated in Figure 3. It is important for mediation analysis to be conducted according to a hypothesized model rather than as an exploratory exercise (Johansson & Høglend, 2007). Accordingly, it would be expected that studies would assess models of mediation to match the stated hypothesized pathways. One paper presented two contrasting hypothesized pathways (represented by *a* and *c* in Figure 3; Lackner *et al.*, 2007). However, the final model that was evaluated includes additional paths incorporating QoL. This appears to be exploratory modelling aiming to achieve the second aim of the paper, which was stated as 'to examine the interrelationships amongst symptom improvement, QoL and distress'. Another paper did not state a directional hypothesis regarding which variables were likely to mediate treatment effect but rather hypothesized that numerous variables may do so without a pre-specified mediation model (Labus *et al.*, 2013).

Table 1: Study characteristics

Study	Study design	Sample size	Sample (age, gender, diagnostic criteria)	Control group	Theoretical model	Intervention (duration, amount, time period)	Intervention delivery (by nurse, therapist)	Adherence to intervention	Time points of assessment in mediation analysis
Garland *et al.* (2012)	RCT	75	100% female Mean age 42 ROME II criteria Receiving TAU	Support group with psycho-education	MBSR	8 weekly 2-hr group sessions and1 half day retreat. MBSR programme with adaptation for IBS in terms of focal points of meditation and homework including psycho-education on IBS	Certified health coach with 10 years' experience in teaching MBSR in clinical settings	NR	Baseline* Two weeks post -treatment* 3 months
Reme *et al.* (2011)	RCT	149	82% female Mean age 33 GP diagnosed IBS Receiving Mebeverine	Mebeverine alone	CBT	6 weekly 50-min sessions face to face. CBT based on Lang's three-systems model and adapted to IBS in terms of cognitions and behaviours focused upon 270 mg Mebeverine taken 3 times daily in addition	Four general practice nurses trained to deliver CBT	59% received intervention	Baseline * First follow-up at 1.5 months* 3 months 6 months 12 months
Labus *et al (2013)*	RCT	69	72.5% female Mean age 46 ROME II	WL Control	CBT	5 weekly 2-hr group sessions. Intervention consisted of (1) education on neurobiology of stress and IBS in the context of the three-systems CBT model; (2) psychological focus of role of cognitions and behaviours; (3) relaxation training; and (4) homework including symptom diaries and relaxation training	Lead by a gastroenterologist (45% of sessions) and a therapist (55% of sessions).	NR	Baseline* Post-treatment (5 weeks)* 3 months*
Chilcot and Moss-Morris (2013)	RCT	64	73% female Mean age 39 ROME I modified or ROME II Receiving TAU	TAU receiving an IBS fact sheet on how IBS diagnosed	CBT	One 1-hr face-to-face session with a Health psychologist and a comprehensive CBT-based self-management manual divided into seven chapters to be completed over 7 to 8-week period in addition to IBS fact sheet	Self-management intervention with one session with health psychologist	93.5% received intervention	Baseline* Post-treatment (2 months)* 5 months 8 months

Table 1 (*continued*)

Study	Study design	Sample size	Sample (age, gender, diagnostic criteria)	Control group	Theoretical model	Intervention (duration, amount, time period)	Intervention delivery (by nurse, therapist)	Adherence to intervention	Time points of assessment in mediation analysis
Jones *et al.* (2011)	RCT	105	81% female Mean age 42 ROME I	(1) Relaxation therapy (2) TAU	CBT	8 weekly 1-hr face-to-face CBT sessions. Intervention consisted of a manual-based programme incorporating realistic symptom appraisal, enhanced coping strategies, cognitive restructuring, and problem-solving. PTs also received TAU and relaxation training	Clinical psychologist	NR	Baseline* Mid-point (4 weeks)* Post-treatment (8 weeks)* 6 months 1 year
Hunt *et al.* (2009)	RCT	54	81.5% female Mean age 38 Self-report of medical IBS diagnosis	WL Control	CBT	5 weekly Web delivered modules with homework assignments submitted by email. Individualized feedback given within 48 hr. Modules included the following: (1) psycho-education on biological link between stress and GI symptoms and relaxation training; (2) cognitive stress management; (3) catastrophic thinking; (4) graduated exposure; and (5) behavioural experiments	Self-management intervention	62% received active treatment and completed 6-week assessment	Baseline* Post-treatment (6 weeks)* 3 months (for intervention group only)*
Lackner *et al (2007)*	RCT	147	82% female Mean age 48 ROME II	Psycho-educational support. WL Control	CBT	10 weekly 90-min group CBT sessions. Intervention consisted of a manual-based programme incorporating contextual/ situational factors associated with flare-ups, unhelpful cognitions, enhancing coping strategies, and problem-solving abilities	Three clinical psychologists with average of 10 years of experience delivering psychological treatments to painful medical disorders.	90.8% completed active treatment	Baseline * Post- treatment (12 weeks)*

Table 1 (*continued)*

Study	Study design	Sample size	Sample (age, gender, diagnostic criteria)	Control group	Theoretical model	Intervention (duration, amount, time period)	Intervention delivery (by nurse, therapist)	Adherence to intervention	Time points of assessment in mediation analysis
Ljótsson *et al.* (2013)	RCT	195	79% female Mean age 38 ROME III diagnosis	Internet-delivered stress management	CBT	10-week Internet-delivered CBT. Intervention consisted of exposure and Mindfulness exercises, including (1) exposure to symptoms by engaging in behaviours believed to trigger symptoms; (2) reduction in safety behaviours; (3) exposure to behaviours normally avoided when experiencing symptoms; (4) altering of toileting habits; and (5) a range of mindfulness exercises to practice daily. Participants also received regular online support	Therapist/clinical psychologist/psychology graduate student	NR	Weekly from week 1 to10*
Wolitzky-Taylor *et al.* (2012)	RCT	76	74% female Mean age 39 ROME II diagnosis	Attentional Control or Stress management	CBT	10 weekly 50-min sessions. CBT-introceptive exposure intervention based on CBT for panic disorder and adapted for the IBS population. Intervention consisted of (1) psycho-education of brain–gut physiological relationship; (2) attentional control skills; (3) cognitive reframing of specific illness cognitions; (4) interoceptive exposure to IBS-relevant visceral sensations; and (5) exposure to behaviours normally avoided when experiencing symptoms	NR	NR	Baseline* Mid-treatment (week 5)* Post-treatment (week 10)* Follow-up (5 months)

Notes. TAU = Treatment as usual; NR = Not reported. *Time point assessment included in mediation analysis.

Table 2: Treatment models and intervention protocols used.

Study	Treatment Model Explicitly Referenced	Intervention Protocol Components
Garland et al (2008)	Mindfulness Based Stress Reduction tailored to IBS symptoms (Gaylord et al., 2009)	(1) Sitting, walking, yoga and body scan mediations. (2) Mindfulness tailored towards IBS by emphasizing relevance of mindfulness in coping with IBS-related symptoms and perceptions. (3) Psychoeducation component was included regarding the physiological relationship between stress and symptoms (4) Promotion of awareness of sensory versus emotional processing of interoceptive signals, with view to counteract catastrophizing.
Reme et al (2011)	CBT Three systems model (Kennedy et al., 2006b)	(1) Assessment of main symptom, precipitating factors, maintaining cognitions & behaviours, discussion of treatment rationale (2) Monitoring symptoms, behaviours & cognitions and interrelations (3) Long term & short term behavioural goal setting with relation to symptoms- graded exposure (4) Behavioural experiments to test beliefs about consequences of IBS (5) Psychoeducation about stress and bowel symptoms (6) Problem solving and symptom & stress management techniques (7) Managing flare ups
Labus et al (2012)	Biopsychosocial model of IBS	(1) Psychoeducation about stress, IBS self management regarding diet and medication (2) Psychoeducation regarding role of symptom appraisal, beliefs and attitudes and links between cognitions, mood, stress, behavioural responses and symptoms (3) Alternative responses (4) Relaxation exercises (5) Monitoring symptoms, behaviours & cognitions and interrelations
Chilcot & Moss-Morris (2013)	CBT (Moss-Morris et al., 2010)	Treatment rationale explained (2) Monitoring symptoms, behaviours & cognitions and interrelations (3) General consideration of unhelpful cognitions, perfectionism and patterns of boom/bust (4) Long term & short term behavioural goal setting with relation to symptoms- graduated exposure (5) Psychoeducation about stress and bowel symptoms, sleep hygiene (6) Problem solving and symptom & stress management techniques including relaxation techniques (7) Managing flare ups
Jones et al (2011)	CBT/Biopsychosocial model (Jones et al., 2011)	(1) Realistic symptom appraisal (2) Enhanced coping strategies (3) Cognitive restructuring (4) Problem solving

Table 2 (continued)

Study	Treatment Model Explicitly Referenced	Intervention Protocol Components
Hunt et al (2009)	CBT with inclusion of module targeting IBS specific catastrophizing (Hunt et al., 2009)	(1) Psychoeducation about stress and bowel symptoms (2) Relaxation training (3) Monitoring cognitions & emotions (4) IBS specific catastrophizing, thought records & identification of interrelationship between IBS-specific cognitions, behaviours, emotions and symptoms (5) Graduated exposure (6) Behavioural experiments to test beliefs about social consequences of IBS
Lackner et al (2007)	CBT (Blanchard et al., 2007)	(1) Psychoeducation about stress and bowel symptoms (2) Monitoring symptoms, behaviours & cognitions and interrelations (3) Problem solving and symptom & stress management techniques (4) Relaxation training (5) cognitive restructuring for modifying faulty threat appraisals that underlie physiologic and emotional reactivity
Ljotsson et al (2013)	Exposure Based Cognitive Behavioural Therapy (Ljótsson et al., 2011)	(1) Mindfulness exercises to promote awareness of interrelationship between GI symptoms, cognitions, emptions, behaviours/behavioural impulses (2) Exposure exercises & behavioural experiments
Wolitzky et al (2012)	Adapted protocol of CBT for panic disorder (DeCola, 2001, Craske and Barlow, 2006)	(1) Cognitive restructuring of IBS specific beliefs (2) Exposure exercises & behavioural experiments (3) Attentional control skills to reduce symptom focussing

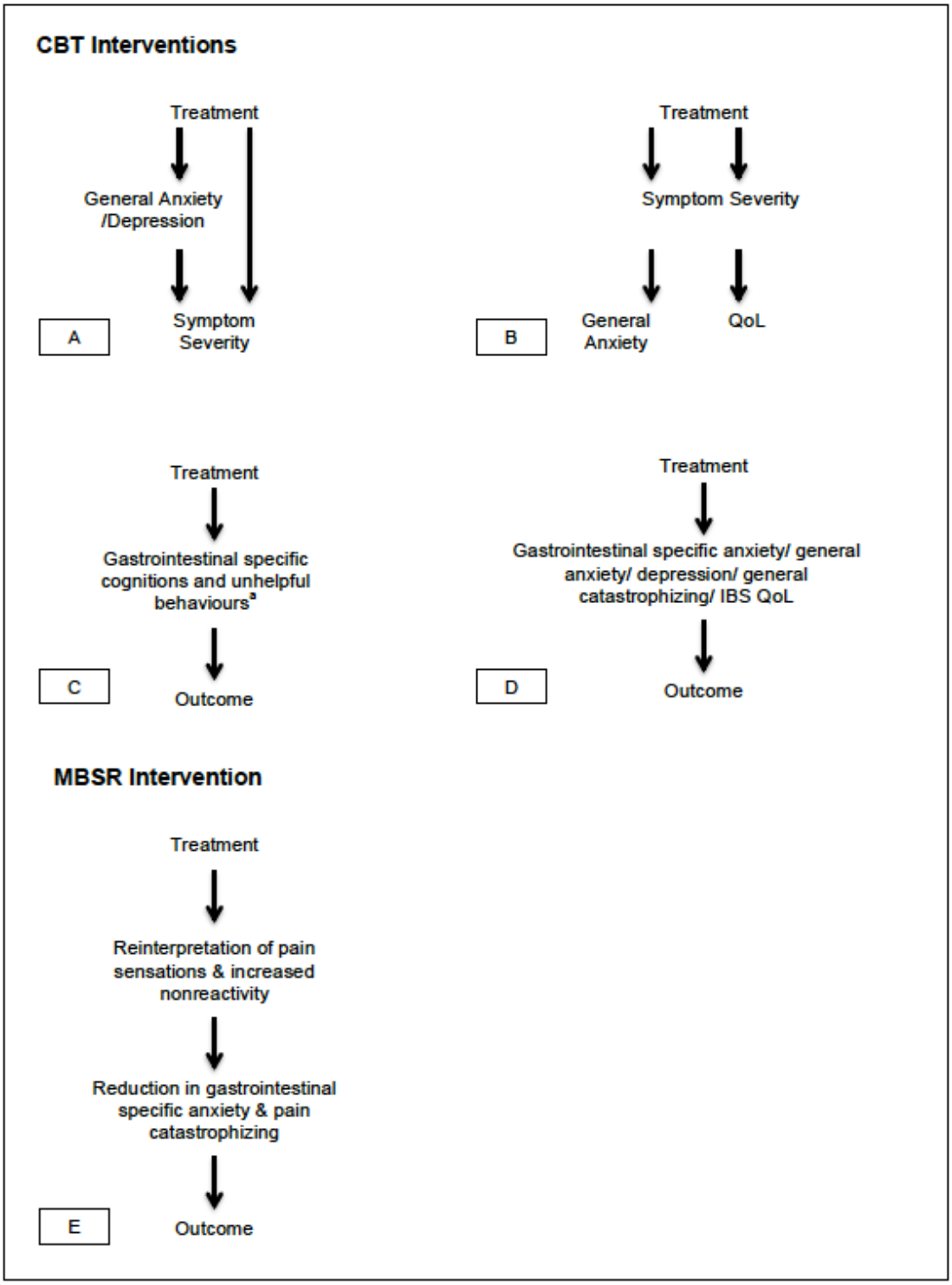

Figure 3: Hypothesized mediated pathways; The diagrams illustrate the hypothesized mediation pathways across papers included in review. The letters indicate which hypothesized pathways were identified in which papers. A. (Jones *et al.*, 2011; Lackner *et al.*, 2007) B. (Lackner *et al.*, 2007) C. (Chilcot & Moss-Morris, 2013; Reme *et al.*, 2011) D. (Hunt *et al.*, 2009; Labus *et al.*, 2013; Ljótsson *et al.*, 2013; Wolitzky-Taylor *et al.*, 2012) E. (Garland *et al.*, 2012). [a] = Reme *et al.* (2011) included gastrointestinal specific behaviours and Chilcot & Moss-Morris (2013) included general unhelpful behaviours.

Mediators

Results of analyses are grouped by the specific mediator variables entered into the models.

Mediators of treatment effect on symptom severity outcome

Perceived stress

One study assessed perceived stress as a mediator of treatment effect (Labus *et al.*, 2013). This was not a significant mediator.

Cognitions & metacognitions

Four studies investigated whether both cognitions and general anxiety/psychological distress mediated the treatment effect (Chilcot & Moss-Morris, 2013; Garland *et al.*, 2012; Hunt *et al.*, 2009; Labus *et al.*, 2013). Of these, three found that cognitions rather than anxiety mediated the treatment effect (Chilcot & Moss-Morris, 2013; Garland *et al.*, 2012; Hunt *et al.*, 2009), whilst one did not (Labus *et al.*, 2013). Of these studies, one study assessed all mediators simultaneously (Garland *et al.*, 2012) and three conducted mediation analyses for each mediator separately (Chilcot & Moss-Morris, 2013; Hunt *et al.*, 2009; Labus *et al.*, 2013).

In addition, one study assessed cognitions as a mediator of treatment effect without a measure of anxiety/psychological distress. This found that cognitions significantly mediated symptom severity along with behaviours (discussed below; Reme *et al.*, 2011). The types of cognitions that mediated treatment effects included negative illness- specific beliefs (Chilcot & Moss-Morris, 2013; Reme *et al.*, 2011), pain-specific catastrophizing (Garland *et al.*, 2012), and general catastrophizing (Hunt *et al.*, 2009; Table 3). The illness-specific beliefs measure used by Chilcot and Moss-Morris (Chilcot & Moss- Morris, 2013) was the Brief Illness Perception Questionnaire tailored to IBS. This measured beliefs about the chronicity, seriousness, and controllability of IBS symptoms The Cognitive Scale for Functional Bowel Disorders (CSFBD), used by Reme *et*

al. (2011), measured the degree of unhelpful beliefs about IBS, with specific items about interpretations of bowel symptoms and reactions to them. Metacognitions were also found to be significant mediators of treatment effect (Garland *et al.*, 2012). These included non-reactivity and reinterpretation of pain.

General anxiety or psychological distress

Of the three studies that investigated the mediating role of anxiety, one found a significant mediated effect in participants who had low baseline QoL (Labus *et al.*, 2013) and one did not demonstrate a significant indirect effect of anxiety (Jones *et al.*, 2011). The third did not report confidence intervals, effect sizes, or significance levels of the path containing distress as a mediator (Lackner *et al.*, 2007; Table 3). The extent to which the model fit the data was also not reported in this study.

Jones *et al.* (2011) tested whether both anxiety and depression had a mediating role in a path model that included a feedback loop from anxiety and depression to symptom severity, and a direct path from treatment to symptom severity. The model was not found to fit the data adequately, and individual confidence intervals, effect sizes, or significance levels were not reported for individual indirect effects for either variable. Labus *et al.* (2013) also investigated the mediating role of depression but found no significant mediation.

Gastrointestinal-specific anxiety

Two studies assessed the GSA utilizing the Visceral Sensitivity Index (VSI; Labus *et al.*, 2004) individually as a mediator of treatment effects (Ljótsson *et al.*, 2013; Wolitzky- Taylor *et al.*, 2012) both finding significant mediation. One found that reduction in GSA mediated treatment effect for the intervention group, but this did not differentiate from the two comparative control groups (Wolitzky-Taylor *et al.*, 2012).

In the three other studies in which GSA was included as a mediator along with other variables, one found it to be a significant mediator along with other cognitive and metacognitive measures (Garland *et al.*, 2012). One study used an alternative measure to the VSI and did not find significant mediation of GSA (Hunt *et al.*, 2009). It did however conclude that there

was marginal mediation with indirect effects yielding a significance of P = .09. The third study did not find GSA to be a significant mediator (Labus *et al.*, 2013).

Behaviours

Behavioural responses were assessed as mediators in two CBT-IS studies, one assessing CBT delivered face to face (Chilcot & Moss-Morris, 2013; Reme *et al.*, 2011) and one evaluating a self-management CBT intervention with some minimal face to face and telephone therapist contact (Chilcot & Moss-Morris, 2013). The former measured behaviours specific to IBS, such as checking stools for abnormalities and avoidance of social events due to bowel symptoms (Reme, Darnley, Kennedy, & Chalder, 2010). The latter measured all-or-nothing and resting/avoidance behaviours related generally to illness but not specifically IBS. These were not found to mediate treatment effect, whereas behaviours specific to IBS did significantly mediate. IBS-specific behaviour was found to be a significant mediator in a path following this sequence: treatment→behaviours→cognitions→symptom severity. This model was found to fit the data better than a change in cognitions preceding a change in behaviour. It must, however, be noted that the analysis lacked temporal precedence limiting the inferences about order of causality of these mediators. The authors stated that mediation was conducted utilizing two time points instead of three, as there was no further change at the third time point.

QoL

One study found this to significantly mediate treatment effect for participants with low baseline QoL, but not for those with medium-to-high baseline QoL (Labus *et al.*, 2013).

Mediators of treatment effect on QoL outcome

Five of the studies (Chilcot & Moss-Morris, 2013; Garland *et al.*, 2012; Hunt *et al.*, 2009; Lackner *et al.*, 2007; Reme *et al.*, 2011) assessed mediation of treatment effects on QoL outcomes, including impaired functioning as measured by the Work and Social Adjustment Scale (Mundt, Marks, Shear, & Greist, 2002). Change in IBS-specific cognitions appeared to mediate change in outcome, with three of four studies assessing cognitions as a mediator of

treatment on QoL, finding significant mediation (Chilcot & Moss-Morris, 2013; Garland *et al.*, 2012; Reme *et al.*, 2011; Table 3). One study found no mediation through anxiety or general and IBS-specific catastrophizing cognitions (Hunt *et al.*, 2009), and another found that reduction in symptom severity mediated improvement in QoL (Lackner *et al.*, 2007). The latter model found significant paths from CBT → symptom severity → QoL → distress → QoL.

Table 3: Results

Study	Outcome variable/s	Main effect analysis	Mediator variables	Effect of intervention on mediators	Mediation analysis	Indirect effects tested	Results: Mediating effects on symptom severity (SS)	Results: Mediating effects on QoL
Garland *et al.* (2012)	• IBS Symptom Severity (IBS-SSS) • IBS-Related Quality of Life (IBS-QoL)	RM-ANOVA	Non-reactivity (FFMQ subscale) Pain Catastrophizing (CSQ pain catastrophizing subscale) Visceral Sensitivity (VSI) Reinterpretation of Pain Sensations (CSQ subscale) Psychological Distress (BSI)	Significant improvement in non- reactivity, pain catastrophizing, VSI, cognitive reinterpretation of pain and psychological distress	Path Analysis	5 models mediation models (one full and four partial)	Significant model of full mediation: T→increased reinterpretation of pain and non- reactivity → decreased pain catastrophizing and visceral sensitivity → and increased reinterpretation of pain → reduced SS	T→decreased visceral sensitivity and pain catastrophizing → increased QoL
Reme et al (2011)	• IBS Symptom Severity (IBS-SSS) Work and Social • Adjustment Scale (WSAS) • Anxiety (HADs)	Regression	Behavioural Responses Questionnaire (BRQ) Cognitive Scale for Functional Bowel Disorders (FBD)	Significant improvement in behavioural scores in CBT group Significant improvement in cognitive scores in CBT group – but not after 3-month follow- up	Path Analysis	Compared 2 path models of mediation for full and partial mediation: (1) T → behaviour → cognitions →outcome (2) T → cognitions →behaviour → outcome for each outcome	Partial mediation T→behaviour→cognition → SS with direct path from behaviour → SS	Partial mediation T→ behaviour →cognition → WSAS with direct path from behaviour → WSAS

Notes. ASI = Anxiety Sensitivity Index (Peterson & Heilbronner, 1987); B-IPQ = Brief Illness Perception Questionnaire (Broadbent, Petrie, Main, & Weinman, 2006); BRQ = Behavioural Responses Questionnaires (Reme *et al.*, 2010); BSSS = Bowel Symptom Severity Scale (Boyce *et al.*, 2000); CBSQ = Cognitive and Behavioural Responses to Symptoms Questionnaire (Moss-Morris & Skerrett, 2006); CSQ = Coping Strategies Questionnaire (Rosenstiel & Keefe, 1983); FBD = Cognitive Scale for Functional Bowel Disorders (Toner *et al.*, 1998); MBSR = Mindfulness-based Stress Reduction; FFMQ = Five Facet Mindfulness Questionnaire (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006); GSRS-IBS = Gastrointestinal Symptom Rating Scale (Svedlund, Sjödin, & Dotevall, 1988); Global GI SS = Global Gastrointestinal symptom severity, an analogue scale from 0 to 20 (Labus *et al.*, 2013); GSIBSI = Global Severity Index of Brief Symptom Inventory (Derogatis & Spencer, 1993); HADS = Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983); IBS-QoLa = IBS Quality of Life (Patrick, Drossman, Frederick, Dicesare, & Puder, 1998); IBS-QoL b = IBS-related Quality of Life (Drossman *et al.*, 2000); IBS-SS = IBS Symptom Severity Score (Francis *et al.*, 1997); WSAS = Work and Social Adjustment Scale (Mundt *et al.*, 2002); VSI = Visceral Sensitivity Index (Labus *et al.*, 2004); VAS = Visceral Anxiety Sensitivity, five items developed to assess gastrointestinal-specific anxiety (Hazlett-Stevens *et al.*, 2003).

Table 3 (continued)

Study	Outcome variable/s	Main effect analysis	Mediator variables	Effect of intervention on mediators	Mediation analysis	Indirect effects tested	Results: Mediating effects on symptom severity (SS)	Results: Mediating effects on QoL
Labus et al (2013)	Symptom Severity (Global GI symptom severity)	Repeated-measures GLM	IBS-QoL*b* depression (HADs) anxiety (HADs) Visceral Sensitivity (VSI) Catastrophizing (subscale of CSQ)	Significant positive change at 5 week, and 3-month follow- up of: • IBS-QoL • depression • catastrophizing Significant reduction of • VSI at 5 weeks	Path Analysis	Moderated mediation model: Baseline QoL = moderator entered into mediation model with IBS-QoL HADs, VSI, Catastrophizing entered as M variables and GI Severity as outcome	T → IBS-QoL →SS when baseline IBS- QoL was low T → Anxiety → SS when baseline IBS- QoL was low	N/A
Chilcot and Moss-Morris (2013)	• IBS-SS • WSAS • HADS	ANCOVA	Brief Illness Perception Questionnaire (B-IPQ) Cognitive and Behavioural Responses to Symptoms Questionnaire (CBSQ) Causal symptom attribution HADS	Significant decrease in catastrophizing, damaging beliefs, and fear avoidance subscales (cognitions) of the CBSQ. Significant change in symptom attribution and illness perceptions	Path Analysis	Separate path models conducted for each significant mediator to explore the relationship of T→ M → Outcome (for each outcome)	Partial mediation T → Illness Perception →IBS with direct effect of T→SS SSS	Partial mediation T → Illness Perceptions→ WSAS with direct effect of T →WSAS T →Damaging beliefs → WSAS with direct effect of T→WSAS
Jones et al (2011)	IBS Symptom Severity (BSSS)	RM-ANOVA	Anxiety (HADS) Depression (HADS)	Significant change in anxiety from baseline to mid-point but reversed from mid-point to endpoint	Path Analysis	Path model from T→SS with inclusion of different specified paths involving anxiety and depression	Model not an adequate fit according to chi-square goodness of fit (X^2= 285.9, 29 df, P < .0005). Did not report findings for indirect paths	N/A

Table 3 (continued)

Study	Outcome variable/s	Main effect analysis	Mediator variables	Effect of intervention on mediators	Mediation analysis	Indirect effects tested	Results: Mediating effects on symptom severity (SS)	Results: Mediating effects on QoL
Hunt et al (2009)	IBS Symptom severity (GSRS IBS) IBS QoL	ANCOVA	Anxiety (ASI) GI Specific anxiety (VAS) General catastrophising (subscale CSQ) GI specific catastrophising (subscale CSQ)	Significant change in all outcome and mediating variables post treatment	ANCOVA utilizing Baron & Kenny's framework	All mediator variables tested for indirect effects on symptom severity and IBS-QoL	General catastrophising found to mediate treatment effect of treatment on symptom severity. No other mediation found	N/A
Lackner et al (2007)	• IBS symptom severity (visual analogue scale) • IBS QoL	Two way ANOVA	Psychological distress (BSI) IBS-QoL	Psychological distress reduced (significance not reported) IBS-QoL increased (significance not reported)	Path Analysis	Path model from T→SS, QoL, distress, with bidirectional paths between all three variables to each other.	Model fit not reported. No significant mediation effect on symptom severity reported	Model fit not reported T→SS → IBS QoL
Ljotsson et al (2013)	IBS Symptom Severity (GSRS-IBS)	Parallel process latent growth curve model	Gastrointestinal symptom specific anxiety (VSI) Stress (PSS)	Significant differences in linear growth rate of VSI Stress significantly decreased over time – no difference between groups	Parallel process latent growth curve model	Two separate parallel bivariate growth models conducted: T→ VSI → GSRS-IBS T→PSS → GSRS-IBS	VSI found to significantly mediate the effect of treatment on GSRS	N/A
Wolitzky et al (2012)	IBS symptom severity (a composite bowel symptom severity index, BSSS) IBS-QoL	Hierarchical linear model	Gastrointestinal symptom specific anxiety (VSI)	Significantly reduced GSA.	Hierarchical Linear Model	Group x VSI slope interaction	VSI mediated treatment effect on outcome but not differentially across treatment and control groups.	N/A

Discussion

Summary of results

The review assessed which psychological variables significantly mediated treatment effects on the outcome of symptom severity and/QoL. Eight studies assessed mediation in the context of CBT interventions. The results indicate that both GI-specific cognitive change and GSA are key mechanisms by which psychological treatments have effect on both symptom severity and QoL. Four of five studies assessing cognitions as a mediator found them to mediate the effects of treatment on symptom severity. Three of five studies assessing GSA as a mediator found significant mediation, and one found a trend towards significant mediation. Of the three studies that assessed general anxiety/psychological distress, only one found it to significantly mediate treatment effect (Labus *et al.,* 2013). This study found evidence of moderated mediation, in that anxiety was only found to significantly mediate treatment in participants who had low baseline QoL. The stratification of analysis by QoL does unfortunately reduce the power to detect significant mediators and makes results hard to interpret.

Only two studies assessed behavioural responses as a mediator (Chilcot & Moss-Morris, 2013; Reme *et al.,* 2011); one measuring IBS-specific behaviours found it to be a significant mediator (Reme *et al.*, 2011) and the other, measuring more general all-or- nothing (boom or bust) and avoidance behaviour, did not (Chilcot & Moss-Morris, 2013). Similarly, the trend for mediation of treatment effects on QoL found that changes in cognitions resulted in improved QoL (Chilcot & Moss-Morris, 2013; Reme *et al.,* 2011). Two studies assessed the mediating effect of psychological distress and cognitive factors on QoL. Of these, one found no mediation (Hunt *et al.,* 2009) and the other found that a decrease in GSA and pain catastrophizing resulted in an enhanced QoL (Garland *et al.*, 2012). Lackner *et al.* (2007) found a series of significant paths demonstrating that CBT had direct effects on symptom severity and that this influenced QoL (Table 3). However, the fit of this path model to the data was not reported, and therefore, the results should be interpreted with caution.

Quality of studies

Most studies were classified as moderate-to-high quality in the RCT QA. The two criteria that were most commonly not met were whether the outcome assessor was blinded and whether compliance was described and acceptable. Often it was unclear as to whether the outcome assessor was blind or not, or what the process for collecting outcomes was. In terms of the compliance of participants to the interventions, this was often not described and where it was, it was low. In one study, around 40% of participants were considered not to have completed a full course of therapy (Kennedy *et al.*, 2005; Reme *et al.*, 2011).

Quality as assessed specifically for the mediation analyses was also generally moderate across the studies. All studies included a control group in the analysis, and all studies were designed to influence mediating variables as determined by the inclusion criteria. Around half of the studies failed to account for temporal ordering of mediator change prior to outcome change in the analysis using variables measured at the same time point (Garland *et al.*, 2012; Hunt *et al.*, 2009; Jones *et al.*, 2011; Lackner *et al.*, 2007; Reme *et al.*, 2011). This means that the extent to which causal interpretations can be made is limited. Four studies of seven that used path analysis or SEM did not make clear whether they used more than one assessment of model fit (Chilcot & Moss-Morris, 2013; Jones *et al.*, 2011; Labus *et al.*, 2013; Lackner *et al.*, 2007). Not reporting a range of model fit indices reduces transparency as to whether the model fits the data taking into account different factors such as sample size and model complexity.

Five of the nine studies did not present confidence intervals for the indirect paths (Garland *et al.*, 2012; Hunt *et al.*, 2009; Jones *et al.*, 2011; Lackner *et al.*, 2007; Wolitzky- Taylor *et al.*, 2012). Neglecting to report confidence intervals in any study employing statistical methods renders it uninterpretable; in these cases, it prevents us from gaining insight into the likely values of the mediated effect. Furthermore, a subset of these studies conducted path analysis but did not report path coefficients for the indirect effect (Jones *et al.*, 2011; Lackner *et al.*, 2007). Consequently, interpretations of the size or extent of the mediated effect cannot be made without doing further calculations.

Issues with analysis comparisons

A predominant limitation of the use of the Baron and Kenny framework utilizing a series of regressions is that it has low statistical power as compared to SEM or path analysis (Hayes, 2009; MacKinnon, 2008; MacKinnon *et al.*, 2002; Windgassen *et al.*, 2016). It also does not allow for investigation of more complex mediation modelling investigating whether one mediator precedes another or works simultaneously. Different approaches to mediation analysis make study comparison challenging, as some analyses provide more comprehensive assessment of mediation than others.

Another issue complicating the comparison of mediation studies is the inclusion or non-inclusion of covariates. Some analyses control for covariates such as baseline measures of the outcome, mediator variable, or both. Inclusion of covariates is recommended in order to reduce bias in mediation effect estimates and leads to a greater understanding of the influence of potential confounding variables (MacKinnon & Pirlott, 2015; MacKinnon *et al.*, 2007; VanderWeele, 2015). Less than half of the papers included in the review included covariates in the analysis. It is generally straightforward to adjust for baseline measures of mediators and outcome, which may be amongst the most important confounders of the mediator/outcome relationship.

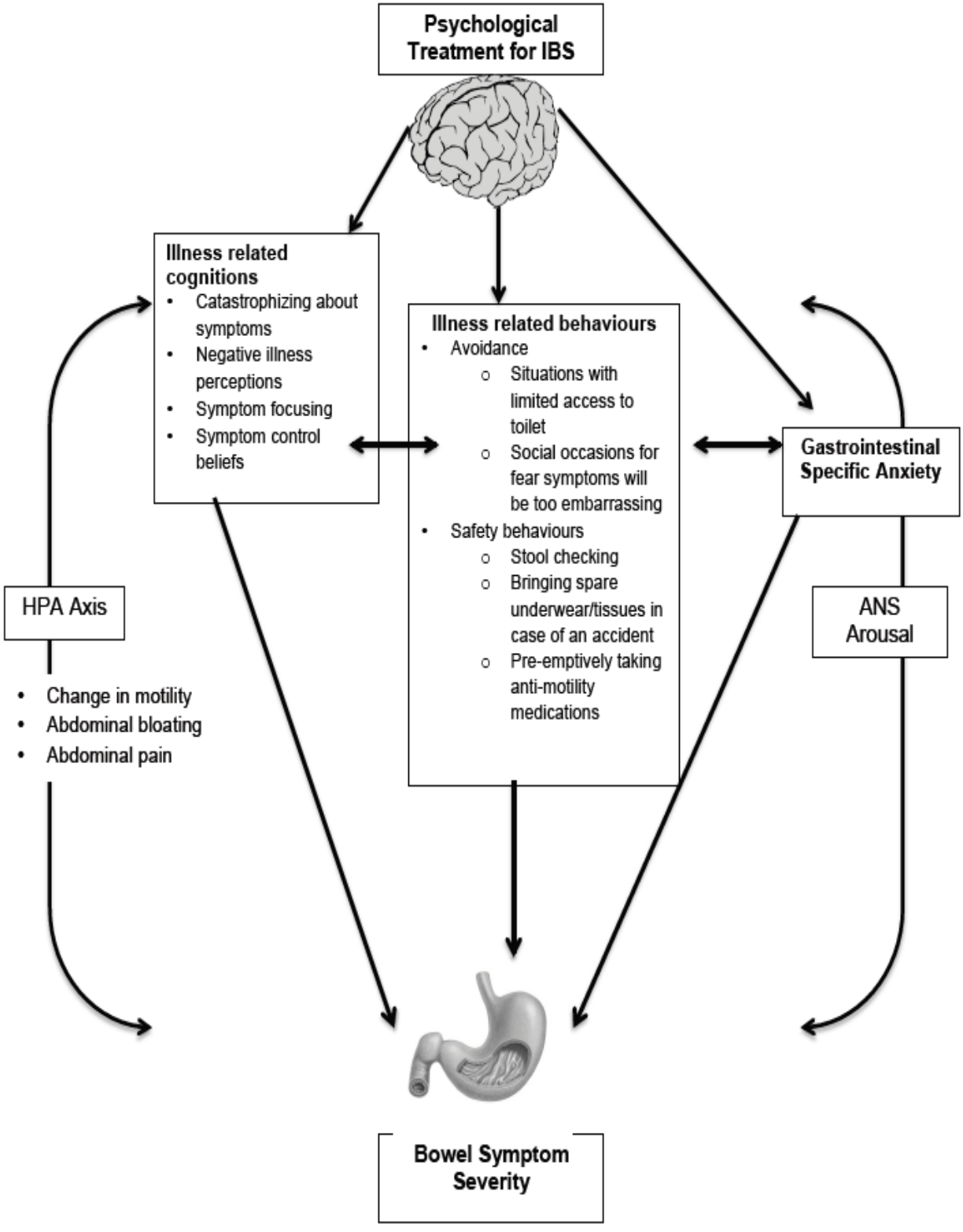

Figure 4: Mediation model of IBS. The figure depicts a hypothesized model of mediation based on the results of the review.

The role of theory

The design of intervention RCTs should be informed by theory, which should include the important mediating variables that are hypothesized to change with treatment and in turn have an effect on outcome/s. It is interesting to note that four of nine papers assessed the mediating role of anxiety/psychological distress, without an inclusion of a cognitive measure. This is despite the fact that the majority of studies referenced a cognitive behavioural model as a basis for informing intervention design.

Gastrointestinal-specific anxiety versus general anxiety

All studies except one (Hunt *et al.*, 2009) measuring GSA utilized the VSI (Labus *et al.*, 2004). The VSI incorporates items that pertain to feelings of anxiety specifically relating to IBS symptoms, as well as IBS-specific cognitions and behaviours. The other measure of GSA was not a validated measure. The authors used items from a general anxiety scale that had been tailored to apply to specific IBS-related symptoms (Hazlett-Stevens, Craske, Mayer, Chang, & Naliboff, 2003). There may be an argument for the development of a scale that specifically measures GSA, without the inclusion of cognitive and behavioural items. Such a measure may allow the elucidation of the relationship between illness-specific cognitions, behaviours, and GSA.

The review suggests that psychological treatments achieve improved outcomes, predominantly by reducing GSA, rather than general anxiety. Analysis conducted by Garland *et al.* (2012) compared a series of path models to assess how well they fit the data. The model including a general measure of psychological distress was found not to fit the data as well as the final model, which included GSA amongst other variables described earlier. It must, however, be acknowledged that there is a high comorbidity of anxiety in IBS populations (Fond *et al.*, 2014). Consequently, it is likely that psychological approaches targeting general anxiety may also achieve a reduction in symptom severity. The distinction between general and GSA is important particularly for treatments provided to individuals with IBS who do not have high general anxiety.

An assimilated model of mediation

A model of mediation for psychological treatment effect is proposed based on the findings of the review (Figure 4). The review finds that both illness-specific cognitions and GSA are predominant mediators of treatment effect. There is also preliminary evidence that illness- specific behaviours have a mediating effect. The paper assessing the role of illness-specific behaviours found that change in behaviours preceded change in illness-specific cognitions (Reme *et al.*, 2011). This may indicate that interventions, targeting IBS- specific behaviour change, are effective because this subsequently results in cognitive change. It must, however, be acknowledged that the study lacked temporal precedence (Reme *et al.*, 2011). This limits the extent to which the sequence of causality can be inferred.

The review opens questions regarding the relationship between illness-specific cognitions, behaviours, and GSA. It seems likely that there is a bidirectional relationship between symptoms of GSA, cognitions, and behaviour. We propose that the relationship between these three variables impact on symptom severity via the autonomic nervous system and HPA axis. These are systems involved in the physiological stress response and key components of the BGA (Figure 4; Kennedy, Cryan, Quigley, Dinan, & Clarke, 2014; Kennedy *et al.*, 2012). This makes intuitive sense as the GSA is likely to be predictive of and predicted by autonomic arousal (Mayer & Tillisch, 2011).

This review does not support the hypothesis that psychological treatments are effective in reducing symptom severity by targeting comorbid anxiety. The implications for psychological treatments delivered for IBS would be that target for change should be illness-specific factors (GSA, cognitions, behaviours) rather than general levels of anxiety.

Less commonly measured mediators

Interestingly, two studies investigated the potential mediating role of QoL on treatment outcome (Labus *et al.*, 2013; Lackner *et al.*, 2007). One assessed whether the impact of treatment on QoL produced a reduction in symptom severity, and the other assessed whether QoL had a mediating role in a path leading from treatment → symptom severity→ QoL→ distress, including a feedback loop to QoL. The hypothesized mediating role between the studies

was therefore rather different. In neither study was a rationale for the investigation of QoL as a mediator presented, although both studies found significant mediation. Intuitively, QoL is generally regarded as an outcome measure rather than a mediator measure.

Variables that were not shown to mediate the effect of treatment on symptom severity were depression (Jones *et al.*, 2011) and perceived stress (Ljótsson *et al.*, 2013). Such results provide a greater understanding of how to focus treatment, suggesting that depression and stress do not necessarily need to be targeted in order to achieve improve outcomes. Further studies assessing these variables as mediators would be required before definitively drawing this conclusion.

Limitations

The review is limited by the small number of meditational studies that have been conducted to date. Perhaps also due to the empirically based nature of CBT, the majority of the psychological interventions included in review were CBT or designed in accordance with a CBT model. The review was therefore not able to explore mechanisms that may be responsible for change in different therapeutic approaches. Furthermore, potential similarities between different treatment approaches cannot be considered.

Another limitation of the literature reviewed was that the degree of mediation effect could not be uniformly compared across studies. Some papers did not report effect sizes for the mediator variables or paths at all, whilst others presented effect sizes for mediating paths rather than individual variables. The review examines objectively whether mediation was found by considering the significance, confidence intervals, and effect sizes available of the indirect effects and path models tested. It does not examine the nuances of individual analyses contained in the discussion of included papers.

Recommendations for future mediation studies

The review highlights the importance of theoretically informed design of mediation studies. Future studies conducting mediation in the context of a psychological intervention should carefully consider what the targets of change are as informed by the prescribed model of treatment. Measurements of these targets for change in the form of validated and reliable questionnaires

should be included in mediation models. This would allow more complete mediation analysis that can accurately assess how well such models fit the data. In the context of mediation studies within psychological treatments for IBS, this would mean that researchers include measurements of anxiety/distress, cognitions, and behaviours.

Based on the results of this review, it would appear important for researchers to further elucidate the relationship between cognitive change and change in anxiety, or more specifically, GI anxiety. It may be useful to understand whether change in one is dependent on change in the other, or whether change is co-occurring. In addition, few researchers have investigated the potential mediating role of illness-related behaviours. Future studies assessing mediation in this area should include a behavioural measure to further understand whether this is an important mechanism for change.

Conclusion

There is a clear indication that cognitive change is important for reducing symptom severity as well as enhancing QoL in IBS. From the minimal investigation into the mechanistic role of behaviour, it seems that the reduction in certain toileting and avoidance behaviour may also be important for improving these outcomes in IBS. Different studies utilized different measures of distress/anxiety with equivocal findings regarding their mechanistic role in psychosocial interventions on outcome. This was further complicated by the use of the VSI, which appears to be a compound measure.

Future mediation studies and models need to include all mediating variables implicated by the theoretical model of treatment. The limited number of studies to date suggests that it is premature to draw conclusions about the need for the modification of treatment practices. However, the review does provide substantial support for the targeting of unhelpful cognitions as a mechanistic process involved in improving outcomes in IBS.

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Supplementary Materials

Supplementary Appendix S1.

Search Stategy across Ovid, PsycInfo, Embase, MEDLINE, PsycArticles and Global Health.

Search terms included [cbt] OR [“cognitive behav$ therap$”] OR [“cognitive therap$”] OR [“behav$ therap$”] OR [“psycholog$ therap$”] OR [psychotherap$] OR [“psycho$ intervention”] OR [“relaxation training”] OR [“mindful$ based cognitive therapy”] OR [mbct] OR [mbsr] OR [“mindful$ based stress reduction”] OR [“mindful$ based intervention”] OR [“acceptance and commitment therap$”] OR [act] OR [“dynamic psychotherap$”] OR [“psychodynamic therap$”] OR [“multicomponent therapy”] OR [“multi-component therapy”] OR [“multicomponent psychotherapy”] OR [“stress manag$”] OR [counsel$] OR [psycho$educat$] OR [“motivational interview$”] OR [“group therap$”] OR [“self$help”] OR [self$manag$] OR [hypno$] AND [“irritable bowel syndrome”] OR [IBS] AND [mediat$] OR [mechanis$].

Supplementary Material Appendix S2

PICOS inclusion & exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Populations	• Irritable Bowel Syndrome participants	• Any other patient population including Inflammatory Bowel Disease
Interventions	• Any psychological or psycho-educational intervention	• No intervention • Pharmacological intervention
Comparators	• Any control group including wait-list controls and placebo intervention controls	• No control/comparative group
Outcomes	• Primary or secondary outcomes relating to symptom severity and or Quality of Life (QoL)/impact on life	• Any other outcomes
Study Design	• Prospective mediation analysis	• No mediation analysis • Cross sectional mediation analysis • Neuroscientific or neuropsychological studies

Supplementary Material Appendix S3

RCT Quality Assessment Table

Study	Random sequence generation	Allocation concealed	Power analysis/Adequate sample size for analysis	Reliable & well validated measures	Appropriate statistical analysis	Groups similar at baseline on important prognostic indicators	Co-interventions avoided	Blinded outcome assessor	Was timing of the outcome assessment in all groups similar?	Compliance described & acceptable	Drop out described & acceptable	Intention to treat analysis	Total
Chilcot & Moss-Morris 2013	1	1	1	1	1	0	0	0	1	1	1	1	9
Garland et al 2008	1	1	1	1	1	1	0	0	1	0	1	1	9
Hunt et al 2009	0	0	0	1	1	1	0	0	0	0	0	1	4
Jones et al 2011	1	1	0	1	1	1	1	0	1	0	0	0	7
Labus et al 2012	1	0	1	1	1	0	0	0	1	0	0	0	5
Lackner et al 2007	0	0	1	1	1	1	1	0	1	0	1	1	8
Ljotsson et al 2013	1	0	1	1	1	1	0	0	0	0	1	1	7
Reme et al 2011	1	0	1	1	1	1	0	0	1	0	0	1	7
Wolitzky et al 2012	1	0	0	1	1	0	0	0	1	0	0	1	4

Supplementary Material Appendix S4

Mediation quality assessment

Study	Inclusion of control group in analysis	Were the study methods/procedures designed to influence mediating variables?	Mediator variables assessed for change	Mediation analysis informed by theoretical model	Temporal precedence accounted for in analysis	Covariates included in analysis	Used more than one assessment of fit criteria if path model	Study reports confidence intervals of mediated effect (CIs f0r paths a and if B&K approach, or Cis for indirect path if POC used)	Total	Potential total
Chilcot & Moss-Morris 2013	1	1	1	1	1	1	0	1	7	8
Garland et al 2008	1	1	1	1	0	0	1	0	5	8
Hunt et al 2009	1	1	1	1	0	0	x	0	4	7
Jones et al 2011	1	1	1	1	0	0	0	0	5	8
Labus et al 2012	1	1	1	0	1	1	0	1	6	8
Lackner et al 2007	1	1	1	0	0	1	0	0	4	8
Ljotsson et al 2013	1	1	1	1	1	1	1	1	8	8
Reme et al 2011	1	1	1	1	0	0	1	1	6	8
Wolitzky et al 2012	1	1	1	1	1	1	x	0	6	7

4.3 Summary

There are relatively few studies assessing mediation of treatment effect in the context of psychological interventions for IBS (n=9). Different methods of mediation analysis were used across studies. These methods included a series of regressions utilising the causal steps approach (Baron & Kenny, 1986), path analysis/ structural equation modelling and latent growth curve analysis. A quality assessment criteria for mediation analysis was developed to help contextualise interpretation of results. This assessment criteria can be used as a guideline for informing the mediation analysis to be conducted in study two (chapter five).

Generally mediator variables entered into analysis were consistent with those postulated in the cognitive behavioural models of IBS. These included illness-related and general cognitions, anxiety and behaviours. The results of the review indicate that illness-related cognitions mediate treatment effect, with some evidence to suggest that gastrointestinal specific anxiety (GSA) and illness-related behaviours also mediate treatment effect. The review suggested that changing general anxiety may not be an important target for change in psychological treatments, as only one of three studies found it to be a significant mediator. This study only found significant mediation of general anxiety, when baseline QoL was low. In contrast, three of five studies assessing GSA found it to be a significant mediator, and therefore the results may suggest that this is an important target for change in psychological interventions for IBS.

Further studies are required with sufficient sample sizes to assess whether all potential mediators as identified by the cognitive behavioural models of IBS are indeed significant mediators of change in outcomes. This would involve the assessment of parallel mediation models, which include general and/or GI specific anxiety, GI related cognitions and GI related behaviours as mediators.

5. A Mediation Analysis of Cognitive Behavioural Treatment Effect in Irritable Bowel Syndrome

5.1 Chapter Overview

The systematic review in the previous chapter identified common mediator variables entered into analyses assessing the treatment mechanisms of CBT in IBS. These included GI related cognitions and general anxiety, with only a few studies assessing the role of behaviours as potential mediators of treatment effect. The mediation analysis conducted in study two consequently aimed to assess whether mediators identified in the CB models of IBS did significantly mediate treatment effect. Specifically, the analysis aimed to assess the mediating roles of GI related avoidance behaviours, GI related safety behaviours, GI related cognitions, and general anxiety on the outcomes of symptom severity and work and social adjustment.

An additional aim of study two was to identify which mediating variables changed first in sequential mediator models. It was hypothesized that cognitive and behavioural change would precede change in anxiety, as these were the targets for change in the treatment protocol informed by the three systems model. Furthermore, in the previous mediation study based on the same data, cognitive and behavioural change was found to precede changes in anxiety (Reme, Stahl et al, 2011). In this study, sequential mediation models found that change in behaviours preceded change in cognitions, and that this sequence led to change in the outcomes of anxiety, symptom severity and work and social adjustment.

In the systematic review in study one, some common limitations to analyses were found. These included: (1) lack of temporal precedence of mediating and outcome variables (i.e. these variables were not taken from sequential time points to uphold inferences regarding causality) (2) analysis not being informed by a theoretical model in terms of the design of the mediation analysis (3) analysis not controlling for the potential confounding effects of baseline mediator and outcome variables (4) lack of quantification of indirect effects (i.e. not presenting the path coefficient or confidence intervals of the indirect effect) (5) non-reporting of assessment fit criteria of path models. The analysis conducted in study two therefore aimed to address all of these methodological limitations.

5.2 Submitted Paper

This paper is under peer review in *Behavior Research & Therapy*.

Article Title: Key mechanisms of cognitive behavioural therapy in irritable bowel syndrome: the importance of gastrointestinal related cognitions, behaviours and general anxiety

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Keywords: Cognitive behaviour therapy; irritable bowel syndrome; treatment mechanisms; illness related cognitions; safety behaviours; anxiety; avoidance behaviours

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Abstract

Background: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterised by abdominal pain and altered bowel movements. Cognitive behavioural therapy (CBT) has been shown to be effective in reducing symptom severity in IBS and enhancing quality of life/ functioning. The present study sought to identify how CBT achieves change in these outcomes.

Method: Structural equation modelling was used to conduct a series of simple and sequential mediation models. Avoidance behaviour, safety behaviour, gastrointestinal cognitions and general anxiety were included in simple mediation models to assess whether they mediated treatment effect. Sequential models compared the fit of mediational sequences to identify whether cognitive and behavioural change preceded a reduction in anxiety.

Results: Simple mediation models showed that gastrointestinal (GI) safety behaviours, GI related cognitions and general anxiety mediated treatment effect on the outcomes of symptom severity and work and social adjustment. Avoidance behaviour was not found to be a significant mediator for either outcome. Sequential mediation models indicated that unhelpful GI related cognitions reduced before anxiety did, and this sequential path (R→ GI related cognitions→ anxiety→ outcome) was significant for both outcomes. A reduction in GI safety behaviours were also found to precede a reduction in anxiety. This sequence (R→ GI safety behaviours→ anxiety→outcome) was also significant for both outcomes.

Conclusion: Results suggest that CBT for IBS works by reducing unhelpful GI cognitions and behaviours, which subsequently reduce anxiety. Consequently, psychological treatments for IBS should focus on targeting change in these factors.

Introduction[1]

Irritable bowel syndrome is a functional gastrointestinal disorder characterised by abdominal pain and associated changes in bowel habits (Drossman, 2016). The prevalence of IBS is estimated to be between 10 and 22% in the UK (Kennedy & Jones, 2000; Wilson, Roberts, Roalfe, Bridge, & Singh, 2004). There are no physiological diagnostic markers for IBS and it has long been established as a 'biopsychosocial illness' (Drossman, 1998; Halpert & Drossman, 2005). As such physiological factors such as genetics or infection interact with psychological and social factors such as unhelpful gastrointestinal (GI) related cognitions, anxiety and life stress to result in bowel symptoms and abdominal pain.

The comorbidity of anxiety and depression in IBS is well established (Fond et al., 2014) with a high prevalence of both found in this patient population (Van Oudenhove, Levy et al. 2016). Anxiety and depression have a negative impact on symptom severity and quality of life (QoL) in IBS (Van Oudenhove, Levy, et al., 2016). These affective factors are also associated with negative cognitive patterns such as catastrophising (Knowles et al., 2017; Sherwin, Leary, & Henderson, 2017) and unhelpful illness-related behaviours such as avoidance (Knowles et al., 2017; Wilpart et al., 2017) or over reliance on healthcare services (Whitehead, Palsson, & Jones, 2002). Unhelpful GI related cognitions and behaviours also independently negatively impact on symptoms and QoL in IBS (Van Oudenhove, Törnblom, Störsrud, Tack, & Simrén, 2016; Knowles et al., 2017; Sherwin et al., 2017). Some research would also indicate that these illness-related cognitions and behaviours have a causal role in anxiety and depression (Reme et al., 2011; Knowles et al., 2017; Sherwin et al., 2017; Wilpart et al., 2017).

To date CBT has received the most empirical support for reducing symptom severity and enhancing quality of life in IBS (Ford, Talley, Schoenfeld, Quigley, & Moayyedi, 2009; Ford et al., 2014). Generally CBT involves the targeting of unhelpful cognitions and changing of behavioural responses to symptoms (Windgassen et al., 2017). There

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[1]AIC, Akaike's information criterion; BIC, Bayesian information criterion; CBT, cognitive behavioural therapy; CFI, comparative fit index; GI, gastrointestinal; IBS, irritable bowel syndrome; QoL, quality of life; RCT, randomised controlled trial; RMSEA, root mean square error of approximation ; SEM, structural equation modelling; TLI; tucker-lewis index; WSA, work and social adjustment; χ^2 GOF, Chi Square goodness of fit

are however variations in the cognitive behavioural models applied in IBS (Windgassen et al., 2017). Some focus on the role of GI related cognitions ("*it is extremely embarrassing to keep going to the toilet*") and GI related behaviours (e.g. avoiding situations, checking stools) in the maintenance of symptoms (Kennedy et al., 2005; Chilcot & Moss-Morris, 2013) as based on Lang's three system's model (Lang, Melamed, & Hart, 1970) (appendix A). Others, such as the four-factor CBT model of IBS, focus on reducing GI specific anxiety (Labus et al., 2013) or general anxiety (Blanchard et al., 2007). The different treatments may therefore exert their effects by targeting different mechanisms.

Mediation analysis is a statistical method of identifying the mechanisms of treatment effect. It determines whether change in an outcome is brought about by change in an intermediary variable (a mediating variable) (Mackinnon, Fairchild, & Fritz, 2007; MacKinnon, 2008; Windgassen, Goldsmith, Moss-Morris, & Chalder, 2015). Mediation analysis is important for both advancing theoretical understanding of psychological processes and for refining clinical practice (Mackinnon et al., 2007; Windgassen et al., 2015). Identifying whether hypothesised mechanisms are affected by a treatment approach can provide valuable information about potential avenues for treatment modification.

Previous mediation studies investigating the efficacy of CBT for IBS have assessed a variety of mechanisms (Windgassen, Moss-Morris et al. 2017). Some have shown significant mediating effects of general anxiety (Labus et al., 2013) whilst others have indicated that change in unhelpful illness-related cognitions are the predominant mechanism of treatment effect (Hunt, Moshier, & Milonova, 2009; Garland et al., 2012; Chilcot & Moss-Morris, 2013). Only 2 of 7 studies conducting mediation in CBT for IBS studies included a measure of behaviours in the analysis (Reme et al., 2011; Chilcot & Moss-Morris, 2013). These included all-or-nothing behaviours, which were not shown to meditate treatment effect (Chilcot and Moss-Morris, 2013) and GI related behaviours such as avoiding certain foods or spending excessive time straining on the toilet (Reme, Stahl et al. 2011), which did significantly mediate treatment effect.

The mediation analysis by Reme et al (2011) was conducted in the context of a randomised controlled trial (RCT) comparing the efficacy of an antispasmodic with and without the addition of nurse delivered-CBT in IBS. The CBT delivered was based on the three system's model (Lang et al., 1970), and therefore focussed on changing GI related cognitions and GI behaviours. Sequential mediation models were designed to assess whether cognitive change preceded behavioural change or vice versa for three

outcomes: symptom severity, work and social adjustment (WSA) and anxiety. For all three outcomes the best fitting models involved behavioural change preceding cognitive change. The best fitting model was that for the outcome of anxiety, suggesting that GI related cognitions and GI behaviours in IBS have a causative role in the anxiety experienced in IBS (Reme, Stahl et al, 2011).

The present paper explored the same data as Reme and colleagues (2011) but with some key differences in the approach to address some of the limits of the previous study. Firstly the previous study assessed GI-related behaviours as a unitary measure and not in the composite subscales of avoidance (avoiding certain activities or foods in anticipation or reaction to symptoms) and GI safety behaviours (such as straining to pass a stool or wearing protective undergarments). The previous study also assessed mediation using mediator and outcome measures from the same time points (change between baseline and 1.5 month follow up). Finally, mediation models were tested including only GI related cognitions and GI behaviours as mediators and not anxiety. Therefore the present study sought to fill these gaps with two aims (1) to assess whether GI related avoidant and safety behaviours, GI related cognitions and general anxiety, mediated the effect of CBT on outcomes. It was hypothesized that all four variables would significantly mediate the effect of CBT on both symptom severity and WSA based on the theoretical CBT treatment model and findings from previous studies (Windgassen et al., 2017) (2) to identify which mediating variables changed first in sequential mediator models. We hypothesized that cognitive and behavioural change would precede change in anxiety, as these were the targets for change in the treatment protocol informed by the three systems model (Lang et al., 1970). Furthermore, in the previous study, cognitive and behavioural (assessed as a unitary measure) change was found to cause reduction in anxiety (Reme, Stahl et al. 2011). Mediation models in the present paper were designed to maintain temporal precedence to aid inferences about causality. Therefore models used mediators and outcomes measured at sequential time points. They also assessed GI avoidance and GI safety behaviours as separate mediators of treatment effect, as these are arguably different processes (Beesdo-Baum et al., 2012; Helbig-Lang et al., 2014; Goetz, Davine, Siwiec, & Lee, 2016).

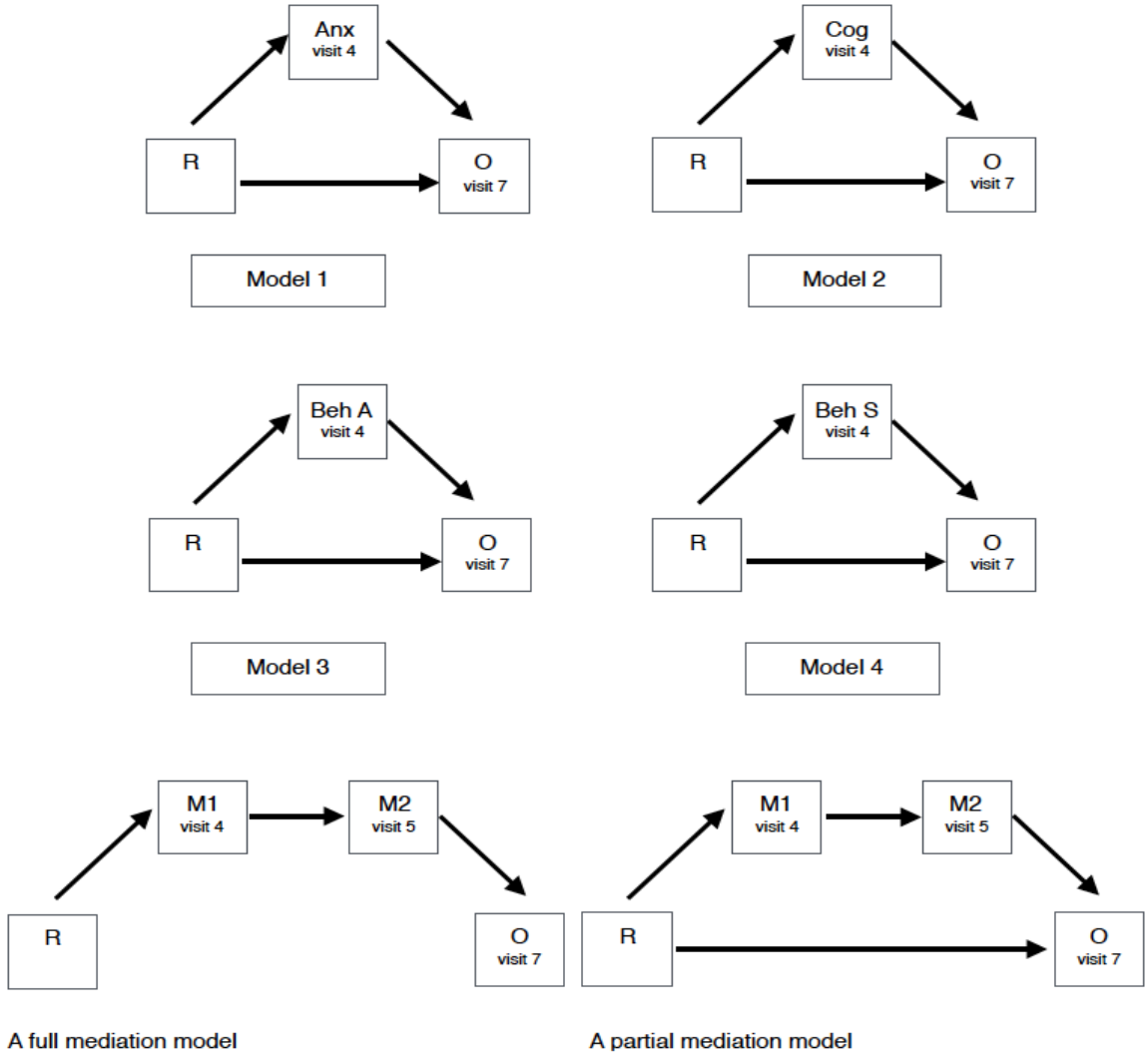

Figure 1: Mediation models tested. Anx, anxiety; Cog, GI related cognitions; Beh A,GI avoidance behaviour; Beh C, GI control behaviour; M1, first mediator in sequence; M2, second mediator in sequence; O, outcome; R, randomisation.

Method

Design

The present study is a secondary mediation analysis of a RCT comparing the effect of CBT plus Mebeverine with Mebeverine alone on symptom severity and WSA outcomes (Kennedy et al., 2005). Results indicated that the addition of CBT improved treatment response up to six months after treatment.

Participants and procedure

Individuals aged between 16 and 50, diagnosed with IBS and meeting the Rome I criteria were recruited from London general practices. A total of 149 participants were randomised to either receive mebeverine alone or to receive CBT in addition to mebeverine (Kennedy et al., 2005). Data of one participant were completely missing, leaving 148 participants for inclusion in the mediation analysis.

Measures were taken at 7 time points, 2 of which were taken 2 (visit 1) and 4 weeks (visit 2) prior to randomisation. The baseline measure was taken just prior to randomisation (visit 3) and the first follow up was taken 1.5 months post randomisation at discharge (visit 4). The second follow up was at 3 months post randomisation (visit 5) and the final follow up at 12 months (visit 7).

CBT treatment

A CBT treatment based on Lang's three systems model (Lang et al., 1970) was developed for IBS (appendix A). The treatment included psycho-education, cognitive restructuring and behavioural techniques such as thought diaries and graded exposure, for example gradually reintroducing avoided foods (appendix B).

Measures

The measures used are listed below, with further detail contained in appendix C. All measures have been shown to be valid and reliable.

Primary Outcomes

The Symptom Severity Scale (SSS) measures symptom severity specific to IBS, and has been found to be sensitive to change over time (Francis, Morris, & Whorwell, 1997).

The Work and Social Adjustment Scale (Mundt, Marks, Shear, & Greist, 2002) is a measure of work and social adjustment (WSA)/functioning.

Mediators

The Cognitive Scale for Functional Bowel Disorders (CSFBD) (Toner et al., 1998) is a measure of GI related cognitions. An example questionnaire item is "my bowel symptoms make me feel out of control".

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) is a general measure of depression and anxiety. Just the anxiety subscale was used to assess general anxiety with items such as "*I feel tense or wound up*".

The IBS Behavioural Responses Questionnaire (IBS-BRQ) (Reme, Darnley, Kennedy, & Chalder, 2010) was used to measure GI avoidance behaviour ("I avoid going out in case I have problems with my IBS") and GI safety behaviour ("I spend more time on the toilet than I would ideally like"). Both types of behaviour are asserted to maintain anxiety in the anxiety and health anxiety literature (Helbig-Lang et al., 2014). However the nature of each behaviour is different. One seeks to exert control over the experience of illness in some sort of way (safety behaviours) and the other relies on withdrawing from certain activities to prevent anticipated troublesome symptoms or experiences (avoidance behaviours).

Statistical Analysis

General

The data were standardised by subtracting the mean of the given scale from each individual's score and dividing by the standard deviation for each given time point. Standardising data reduces potential problems of multicollinearity and allows comparison of indirect effects (Lance, 1988; Frazier, Tix, & Barron, 2004). It has been recommended that mediation variables are assessed for significant change prior to mediation analysis (Lubans, Foster, & Biddle, 2008). For anxiety and GI related cognitions, assessment of main effects and interactions were conducted in the previous mediation paper (Kennedy et al., 2005; Kennedy et al., 2006) and presented again in this paper for contextual clarity. Repeated measures ANOVAs were conducted to assess the main effects of group and time and the interaction (time x group) on the avoidance and safety behavioural subscales of the BRQ, over the three time points included in the mediation analysis (visit 3, 4 and 5). This analysis allowed assessment of whether

change in mediator variables occurred over time, between the treatment and control groups. Significant interactions indicate that there was a change over time, which differed between groups

Mediation models

The mediation models were designed to assess whether the mediators identified in the three systems cognitive behavioural model of IBS (Kennedy et al., 2005), GI-related cognitions and GI behaviours, as well as anxiety, significantly mediated the treatment effect on outcome. Previously Reme et al (2011) found that behavioural change preceded cognitive change, and that this mediational sequence explained change in anxiety. However, the authors used change scores by taking baseline scores from scores at 1.5 month follow up (visit 4) for all mediator measures and outcomes. This limits the causal plausibility of the effects as mediators and outcome were therefore measured using the same time points. In addition, these authors did not assess the potentially different roles of GI related avoidance and safety behaviours. Our models therefore sought to assess whether both types of GI related behavioural responses were mediators of treatment effect. We also sought to identify whether cognitive and behavioural change preceded changes in anxiety for the outcomes of symptom severity and WSA.

Mediation models were fitted in the structural equation modelling (SEM) framework using Mplus version 7. SEM is advocated as an approach that allows simultaneous modelling of several variables, enabling the investigation of more complex mediation models (Mackinnon et al., 2007; MacKinnon, 2008; Hayes, 2009) than would be possible by conducting a series of regressions utilising Baron & Kenny's framework (Baron & Kenny, 1986). Path tracing rules (Kline, 2015) akin to what is specified in the mediation literature were used to calculate indirect effects (MacKinnon 2008).

All mediation models controlled for baseline measures of the mediator and outcome to account for the potential confounding of the non-randomised mediator-outcome relationship, which is widely agreed to be important (MacKinnon, 2008; Emsley, Dunn, & White, 2010; Goldsmith, Chalder, White, Sharpe, & Pickles, 2016). Baseline measures of the mediator and outcome are likely to be amongst the most important confounders (Dunn, Emsley, Liu, & Landau, 2013; Pickles et al., 2015) and may also provide adjustment for other related confounders not included in the model. For most variables, baseline was assessed at visit 3 (pre-randomisation), apart from GI avoidance and safety behaviours where these data were not collected at this time point. In these cases, data from visit 1 was used.

Simple mediation models with single mediators were run first to assess whether the variables identified in the CBT model of IBS significantly mediated treatment effect on outcome (figure 1). Models were run for each potential mediating variable: anxiety, GI related cognitions, GI avoidant and GI safety behaviours. These were run separately for each outcome also.

Sequential mediation models were then run to further elucidate the relationship between cognitive and behavioural processes and anxiety. Specifically, we sought to understand whether it was necessary for cognitive and behavioural change to occur first in order to produce a subsequent reduction in anxiety, ultimately leading to improved outcomes. To assess this we wanted to compare models that had cognitive or behavioural change preceding change in anxiety to models where change in anxiety preceded cognitive or behavioural change.

To allow for causal interpretations of mediational analyses, it is important to ensure that variables are measured in a plausible temporal sequence (Maxwell & Cole, 2007; MacKinnon, 2008; Maxwell, Cole, & Mitchell, 2011; Goldsmith et al., 2016). In other words, to infer that treatment causes change in a mediator and that this change causes subsequent change in an outcome, the mediator should be measured at an earlier time point than the outcome. To this end, the simple mediation models with a single mediator and outcome used mediators assessed at visit 4 (figure 1). In sequential mediator models, the first mediator in the sequence was measured at visit 4 and the second mediator at visit 5. For both simple and sequential mediator models, visit 7 outcome measures were used.

Three types of model fit criteria were used to select the best fitting mediation model. Two absolute model fit indices were used to assess how well models fitted the data (Hooper, Coughlan, & Mullen, 2008). The Chi Square Goodness of Fit (χ^2 GOF) statistic compares the model hypothesized against the saturated model indicating whether they are significantly different. As such a model with good fit should not produce a significant χ^2 statistic. The root mean square error of approximation (RMSEA) is another model fit index that is recommended for small sample sizes (Kline, 2015) . An acceptable fit has been defined as ≤0.08 (Browne & Cudeck, 1993) with a value of ≥1.0 indicating poor fit. Good fit to the data is indicated by a value of ≤0.05 (MacCallum, Browne, & Sugawara, 1996) . The two incremental indices used were the comparative fit index (CFI) and the Tucker-Lewis Index (TLI). Adequate fit of the CFI is indicated by values of ≥0.90 (Marsh, Balla, & Hau, 1996), however more stringent guidelines suggest models should have a value of ≥0.95 for both CFI and TLI (Hu &

Bentler, 1999). Research suggests the CFI performs well with small sample sizes (Tabachnick, Fidell, & Osterlind, 2001). The two information criteria used to compare models were the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC). The AIC allows comparisons between models to choose which of the models considered fits the data best. Differences of >2 between models indicate that the model with the lower AIC value better explains the data (Burnham & Anderson, 2003). The BIC is closely related to the AIC and also penalizes models for the number of parameters included, with lower values indicating a better fit (Burnham & Anderson, 2004).

Final models were selected based on whether they had acceptable or good fit across the majority of the three types of fit indices (absolute, incremental and information) as has previously been recommended (Williams & Holahan, 1994; Marsh & Hau, 1996; Schumacker & Lomax, 2004; Preacher & Merkle, 2012; Preacher, Zhang, Kim, & Mels, 2013), giving priority to the RMSEA, CFI and TLI. This method was designed to tackle the sometimes conflicting criteria and the issues with model selection uncertainty (Preacher & Merkle, 2012). Further details of the analysis are contained in appendix D.

Results

Change in primary outcomes during the course of the trial

There was a significant difference between the groups post treatment (visit 4) on IBS-SSS and WSAS in the CBT + Mebeverine group, compared to Mebeverine alone. The difference between groups, however, was no longer significant by the 6-month follow up (visit 6). The trajectories for both outcomes are illustrated in panel A and B in appendix E. Further detailed results have been reported elsewhere (Kennedy et al., 2005; Kennedy et al., 2006). Conducting mediation even when there is no treatment effect is important as it can clarify why this has happened, for example, if the treatment has not targeting the mediator as expected, or if there is suppression (MacKinnon, Krull, & Lockwood, 2000; Mackinnon et al., 2007), which is when the direct and indirect effect are in opposite directions and cancel each other out (MacKinnon et al., 2000).

Changes in mediating variables: Anxiety, behaviours and cognition

The line graphs in figure 2 depict change in mediator variables over the 3 time points included in the mediation analysis. The changes in anxiety and cognition were previously reported in detail (Kennedy, Jones et al. 2005; Kennedy, Chalder et al. 2006) with a summary of the results presented here for ease. There was a significant main

effect of group but not time on both anxiety and GI related cognitions, indicating that on average over the different follow-up time points anxiety and GI related cognitions were significantly lower in the CBT group than in the control group (figure 2, panels A and B).

Analysis of the behavioural subscales in the present paper found that there was a significant main effect of group on GI safety behaviours $F(1,97) = 12.81$, $p = .001$ with lower levels of GI safety behaviours at follow-up on average in the CBT group. The main effect of time was significant, $F(1.62,156.76) = 4.47$, $p = .019$, which is likely due to the relatively large decrease between baseline and post-treatment ratings of GI safety behaviours in the CBT group. For avoidance behaviours there was no significant main effect of time $F(1.60,154.93) = 2.49$, $p = .098$ or group $F(1,97) = 1.16$, $p = .285$ suggesting that there no difference between the groups on average over the three time points. This may be in part due to the difference between the two groups at baseline, with their profile plots crossing between baseline and post treatment (figure 2, panel C). There were significant group*time interaction effects for all four potential mediator variables (all $p < 0.010$), which was due to the differences in effects between baseline and the two follow-up measurements.

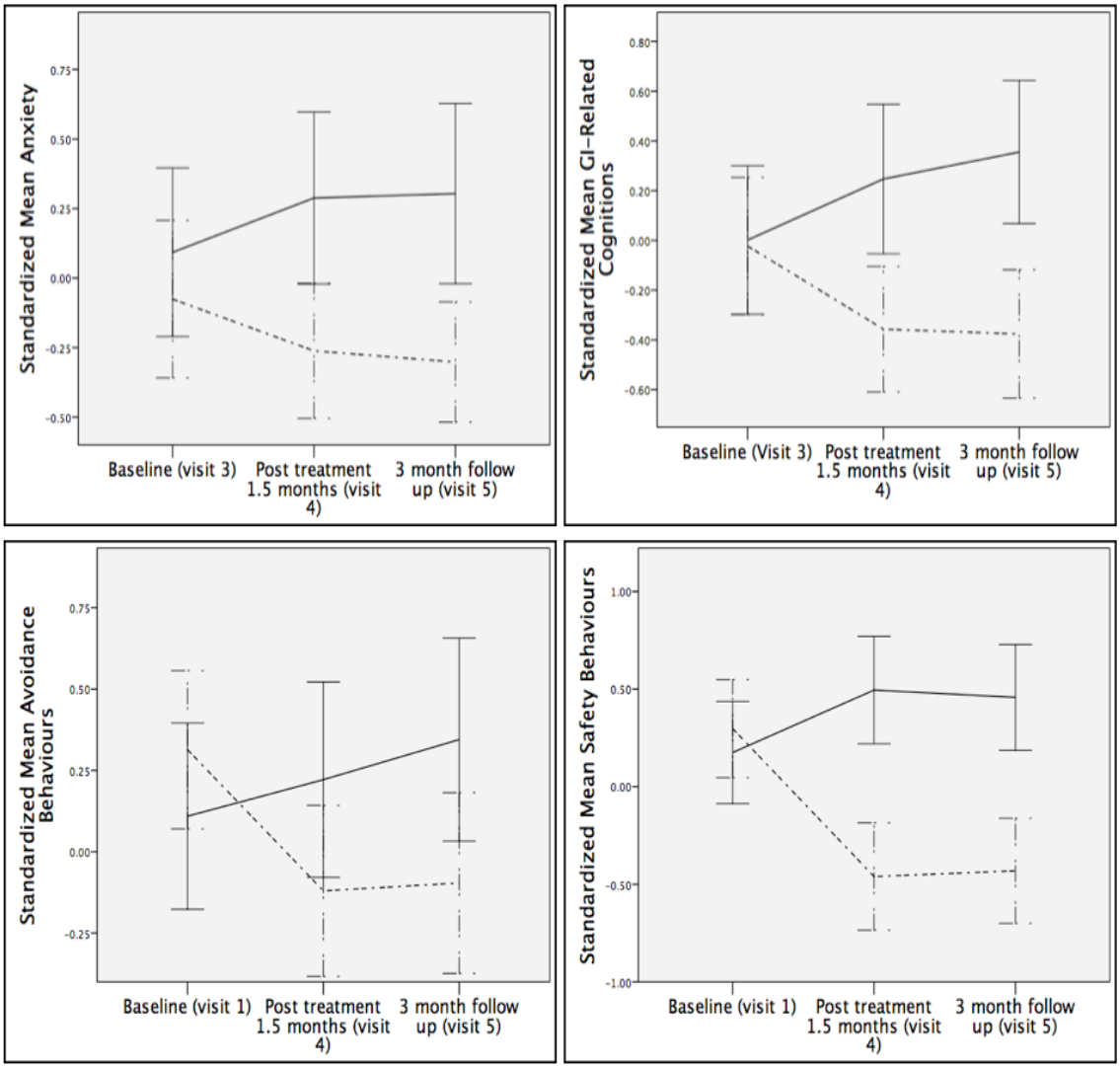

Figure 2: Change over time in mediator variables anxiety (panel A), GI related cognitions (panel B), avoidance (panel C) and control behaviours (panel D) between groups. 95% confidence intervals plotted for each time point.

Simple mediation models

The four variables of interest as mediators, GI related cognitions, avoidance behaviour, safety behaviour and anxiety were initially studied using simple mediation models.

Simple mediation models, each in turn including anxiety, GI related cognitions and GI safety behaviours, fitted the data well (table 1). Anxiety significantly mediated the effect of treatment on symptom severity (-0.26, -0.46 to -0.11, p =0.004) and WSA (-0.35, -0.56 to -0.16, p=0.001). GI related cognitions were a significant mediator of CBT treatment on symptom severity (-0.24, -0.43 to -0.09, p=0.005) and WSA (table 2). Safety behaviour was also a significant mediator for symptom severity (-0.33, -0.57 to -0.11, p=0.005) and WSA (-0.35, -0.60 to -0.14, p=0.004). Avoidance behaviour did not mediate the effect of treatment on either outcome (table 1). Figure 3 shows the standardized indirect effects with the 95% confidence intervals across the four mediators tested. The mediated effects were negative as we expected, because they are products of the negative effect of the treatment on the mediator and the positive effect of the mediator on the outcome. CBT compared to control gave a negative parameter estimate for the effect of the treatment on the mediator, i.e. the mediator values were lower (better) on average in the CBT group compared to the control group. The effect of the mediator on the outcome gave a positive effect estimate because for every standard deviation increase in the mediator (worsening), there was an increase (worsening) in the outcome. The significant indirect effects were similar sizes.

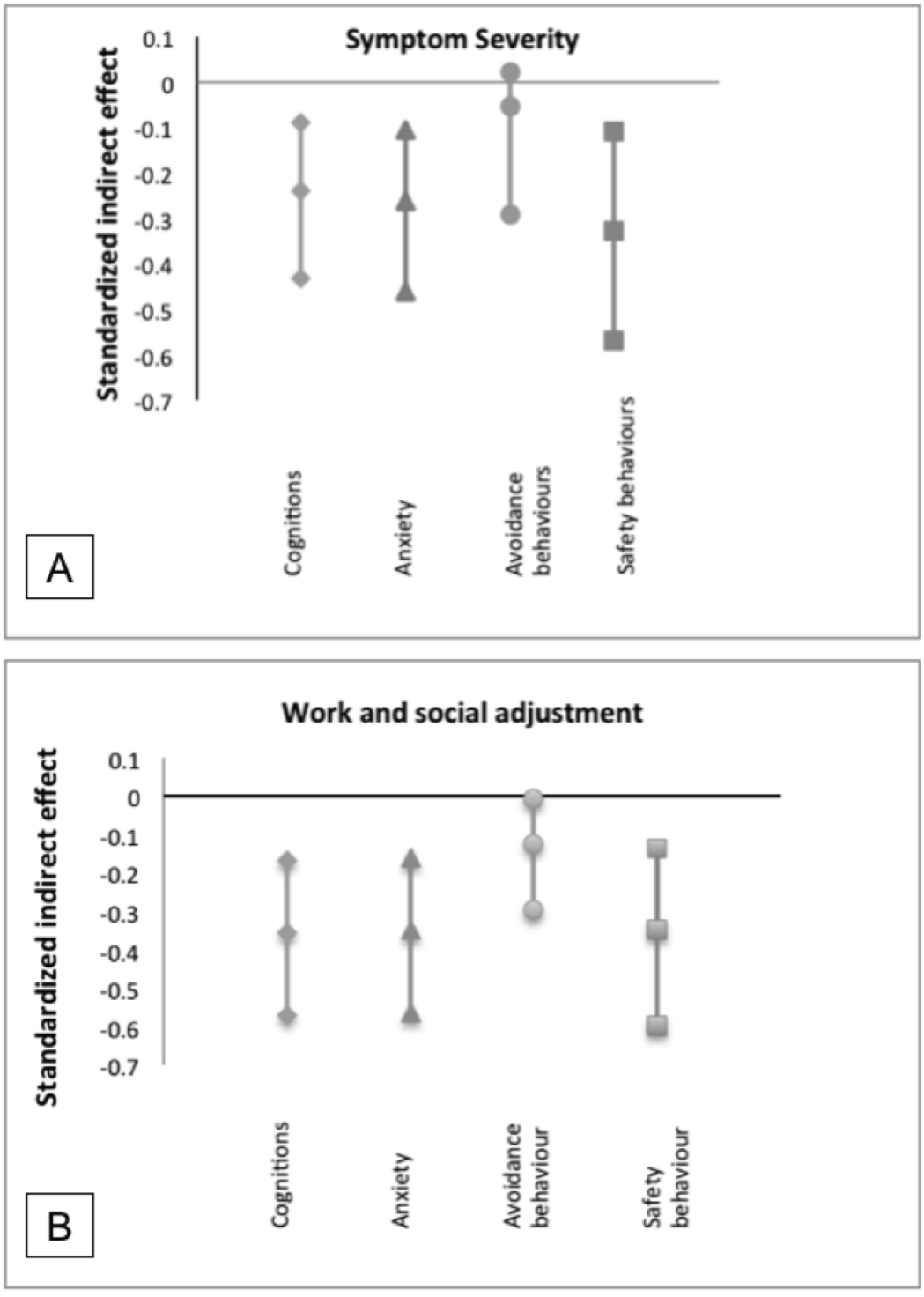

Figure 3: Standardized indirect effects for each mediator variable in simple mediation models with 95% confidence intervals. A) Symptom severity outcome, B) Work and social adjustment outcome.

Sequential Mediation Models

Full and partial mediation models

Comparisons of sequences modelled as full or partial mediation models for the outcome of symptom severity showed that full mediation models fit the best for all mediation sequences (appendix G) apart from the sequence R→anxiety→GI safety behaviours→ symptom severity (model 8a, table 1), where there was little difference in the fit of the models. Comparisons of full and partial mediation models on the WSA found that all sequences fit better as full mediation models (models 5b to 8b, table 1). While most of the differences seen in AIC and BIC between full and partial models were greater than two units, they were generally small (appendix G).

GI related cognitions and Anxiety

In line with our hypothesis, the sequence R→GI related cognitions→anxiety→ symptom severity (appendix F, panel A) showed the best fit to the data with a good fit according to the χ^2 GOF and the CFI model fit criteria (table 1, model 5a). The lower AIC and BIC of 61 and 57 units respectively indicated that change in GI related cognitions preceding change in anxiety was more plausible than change in anxiety preceding change in GI related cognitions. The indirect effect was significant (-0.22, -0.40 to -0.90, p=0.005) and indicated that reduction in unhelpful GI related cognitions, resulted in a reduction of anxiety and this lead to the subsequent reduction in symptom severity (table 2). The same sequence was found to have the best fit for the outcome of WSA as well (appendix F, panel B), with lower AIC and BIC criteria (table 1, model 5b). The indirect effect here was also significant (-.26, -.44 to -.11, p=0.003). For both outcomes, the path R→GI related cognitions→anxiety→outcome had the largest standardised indirect effect compared across all sequential mediation models (figure 4).

Behaviours and Anxiety

As avoidance behaviour was not a significant mediator in the basic mediation models, this was not taken forward into a sequential model, and only GI safety behaviours were studied. Concurrent with our hypothesis, the sequence R→GI safety behaviours→ anxiety→symptom severity fit the data best (appendix F, panel B). This had a good fit according to the CFI and χ^2 GOF and an acceptable fit according to the RMSEA and TLI (table 1, model 7a). However, the AIC and BIC relatively weak support for the model where anxiety preceded GI safety behaviours, conflicting somewhat with the results of the other fit indices (table 1, model 8a). On balance we proceeded with the GI

safety behaviours→anxiety model, where the indirect effect was significant (-0.11, -.24 to -.01, p=.049) with improvement (decrease) in GI safety behaviours and anxiety causing an improvement (decrease) in symptom severity (table 2).

This sequence (R→GI safety behaviours→anxiety→outcome) was also shown to fit the data best for WSA (appendix F, panel D). The CFI indicated good fit and the RMSEA indicated acceptable fit, however the TLI, χ^2 GOF did not indicate good model fit (table 1, model 7b). As for symptom severity, the AIC and BIC provided more support for the reverse sequence (R→anxiety → GI safety behaviours) mediation model. Having given priority to RMSEA and CFI values, we therefore took forward the mediation model with superior RMSEA and CFI values (R→GI safety behaviours→ anxiety→outcome). We found that the indirect effect was significant (-0.12, -.23 to -.03, p=.025) indicating that as mediating variables decreased, WSA also decreased (table 2).

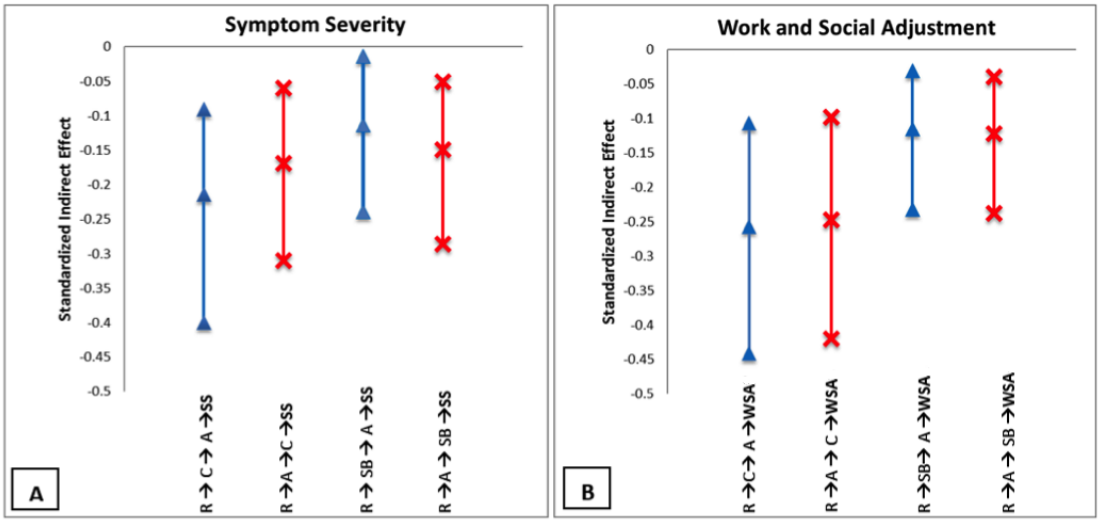

Figure 4: standardised effect sizes of the indirect effects testing in sequential mediation models with 95% confidence intervals. Panel A: outcome of symptom severity. Panel B: outcome of work and social adjustment. R, randomisation, C, GI related cognitions, A, anxiety, SB, GI Safety Behaviours, SS, symptom severity, WSA, work and social adjustment

Discussion

Our paper aimed to establish whether illness-related cognitions, avoidance and safety behaviours and anxiety were significant mediators of treatment effect on the outcomes of symptom severity and WSA. Change in GI related cognitions, GI related safety behaviours and general anxiety were found to mediate the effect of CBT on both outcomes. However, avoidance behaviour was not a significant mediator. The secondary aim of the paper was to elucidate whether there was a particular sequence of change in

cognitive and behavioural processes and changes in anxiety. The results indicated that CBT reduced unhelpful GI related cognitions and that this reduced anxiety. This sequence was found to best explain the treatment effect on both outcomes. Reductions in GI related safety behaviours were also found to precede reductions in anxiety for both outcomes, indicating that change in GI related cognitions and behaviours are necessary to reduce both anxiety and consequently symptom severity and impaired WSA.

Targeting mediators informed by the CBT model

The CBT in this trial was based on a three systems model (Lang, Melamed et al. 1970), targeting change at unhelpful GI related illness cognitions and behaviours. The model suggests that GI related cognitions, behaviours and physical sensations (IBS symptoms as well as physical symptoms of anxiety) are interrelated and that making a change in one response brings about a change in others. The results of our basic mediation analyses provided some support for the model as GI related cognitions and GI safety behaviours along with anxiety were found to significantly mediate the treatment effect. The finding that avoidance behaviour was not a significant mediator was surprising. The paths from avoidance behaviour to outcome in both of the simple mediation models were not significant, suggesting that change in avoidance behaviour was not related to outcome. In contrast, significant R→avoidance behaviour paths at visit 4 indicated that CBT at least initially reduced avoidance behaviours (table 2). The findings may therefore suggest that changing avoidance behaviours does not result in reductions in symptom severity or enhanced functioning. Nevertheless the results demonstrate the importance of GI safety behaviours in the maintenance of symptoms and disruption to work and social functioning in IBS. Safety behaviours such as excessive straining on the toilet or the use of medications to prevent symptoms have been shown to further disrupt bowel functioning and motility (Drossman et al., 1988; Tack, Fried, Houghton, Spicak, & Fisher, 2006). Furthermore, individuals with IBS have reported that engaging in behaviours such as taking preventative medication and wearing protective underwear has a substantial impact on their daily lives (Rønnevig, Vandvik, & Bergbom, 2009; Farndale & Roberts, 2011). As such the results give support to the necessity of changing such behaviours to improve both bowel symptom severity and work and social functioning.

Gastrointestinal related cognitions, GI safety behaviours and anxiety

Our hypothesis was that GI related cognitions and GI safety behaviours would change prior to a reduction in anxiety. Both GI related cognitions and GI behaviours were targeted through the provision of psycho-education (about the interplay between the brain and the gut), cognitive restructuring (thought diaries, recognising and challenging automatic negative thoughts) and goal setting (to change GI avoidance and safety behaviours). Whilst change in anxiety may also be a key process by which treatment causes change in the outcome, and a desired effect of causing cognitive and behavioural change, it was not the target of treatment. The results of the sequential mediation models generally supported our hypothesis. We found that reductions in GI related cognitions such as "*I cannot function normally when I get bowel symptoms*", led to decreased anxiety, with a consequent reduction in the severity of their symptoms. This fits with the wider literature, which suggests increased levels of anxiety are directly associated with worse symptom severity (Simrén et al., 2001; Hazlett-Stevens, Craske, Mayer, Chang, & Naliboff, 2003; Tack et al., 2006; Labus, Mayer, Chang, Bolus, & Naliboff, 2007). This sequence of change (R→GI related cognitions→anxiety→outcome) also makes intuitive sense in explaining the treatment effect on WSA. The less individuals experience anxiety (as a result of reduced unhelpful GI related cognitions), the more likely they are to participate fully in their daily lives across work and social situations (Wells, 1999).

We also found support for the hypothesis that change in GI safety behaviours would precede change in anxiety for both outcomes (R→ GI safety behaviours→ anxiety→ outcome). This provides further corroboration for the three system's model. Although this theoretical model presents the relationship between the variables as bidirectional, the CBT therapy applied in this trial targeted GI safety behaviours (along with other behaviours and GI related cognitions) as a means of reducing anxiety, bowel symptoms and enhancing functioning. Our results fit with previous research in the context of anxiety disorders and health anxiety, which has suggested that targeting the use of safety behaviours is important for the reduction of anxiety (Beesdo-Baum et al., 2012; Helbig-Lang et al., 2014; Goetz et al., 2016) and improving illness trajectories (Olatunji, Etzel, Tomarken, Ciesielski, & Deacon, 2011).

Limitations

Our analysis was conducted in the context of a waning treatment effect at visit 7 (12 month follow up) to preserve temporal sequencing of variables (Kennedy, Chalder et al.

2006). Future mediational studies with similar follow up periods are needed to ascertain whether the results are replicated when the treatment effect is still observed. Nevertheless, assessing mediation in the context of no treatment effect is now widely considered valid and important (Shrout & Bolger, 2002; Emsley et al., 2010; Goldsmith et al., 2016). It allows us to gather information about where in the theoretical mediation pathway our treatment fails. This can help us to refine and improve treatments.

The final models with best fit were the full mediation models, which may in part be due to the lack of a sustained treatment effect i.e. there were no direct effects of treatment on outcome, yet there were significant indirect effects. It is, however, unlikely that our models included all possible mediators. We assessed two-mediator sequences, however other CBT theoretical models, such as the four-factor model suggests at least 3 mediators (GI related cognitions, behaviours and anxiety). Future analysis would ideally include all hypothesised mediators in a model. Our study was also limited by a relatively small sample size, which may increase the probability of type II error (Fritz & MacKinnon, 2007).

A final limitation of the present study is the lack of a GI specific measure of anxiety such as the visceral sensitivity index (Labus et al., 2004). Our previous systematic review suggested that this may be an important mediator of treatment effect in IBS (Windgassen, Moss-Morris et al. 2017).

Strengths

The present study used robust methodology to study the mediation effects of CBT in IBS. Unlike other studies reviewed (Windgassen, Moss-Morris et al. 2017), the inclusion of mediator variables were theoretically informed and assessed at adequate intervals to allow temporal precedence, increasing the plausibility of interpreting effects as causal. Effects of baseline mediators and outcomes on the mediated effect and outcome were controlled for, to reduce the potential for residual confounding of the non-randomised mediator → outcome relationships in the models. In addition, the mediation analysis was conducted using data from a RCT, which further reduces the potential for confounding factors where the treatment is randomised.

Conclusion

Our results suggest that first changing GI related cognitions and GI safety behaviours, leading to a decrease in general anxiety is necessary for cognitive behavioural therapy to reduce symptom severity and the impaired work and social functioning. Avoidance

behaviours were not found to mediate the effect of CBT on either outcome. Our hypothesis that reduction in anxiety followed cognitive and behavioural change for all models was supported.

Table 1: Mediation analysis of symptom severity & work and social adjustment scores with Randomisation (R), Anxiety (A), GI related cognitions (C), GI Safety Behaviours (SB), Symptom Severity (SS) and Work and Social Adjustment (WSA)

	Model (+ baseline)		RMSEA [90% CI]	CFI	TLI	AIC	BIC	χ^2 **GOF**	Indirect effect *p*
Basic Mediation Models	Symptom Severity								
	1a	R→A-→SS	0 [0, 0.15]	1.0	1.02	1616.5	1670.5	$\chi^2(2)=1.36$, p=0.508	.002
	2a	R→C-→SS	0 [0, 0.06]	1.0	1.05	1538.8	1592.8	$\chi^2(2)=0.18$, p=0.915	.005
	3a	R→AB→ SS	0.041 [0, 0.17]	0.996	0.984	1594.8	1648.7	χ^2 (2)=2.49, p=0.287	.19
	4a	R→SB→ SS	0 [0, 0.15]	1.0	1.01	1616.2	1670.2	χ^2 (2)=1.62, p=0.445	.005
Sequential Mediation Models	5a	R→C→A-→SS*	0.070 [0, 0.14]	0.981	0.952	2111.6	2198.5	$\chi^2(6)=10.38$, p=0.109	.006
	6a	R→A→C-→SS*	0.102 [0, 0.17]	0.949	0.872	2174.0	2260.9	$\chi^2(6)=$ 15.20, p=0.019	.010
	7a	R→SB→A →SS*	0.08 [0, 0.15]	0.976	0.939	2218.9	2305.8	$\chi^2(6)=$ 11.17, p=0.083	.049
	8a	R→A→SB→ SS	0.119 [0.05, 0.19]	0.954	0.862	2200.6	2290.5	$\chi^2(6)=$ 15.14, p=0.009	.014

Rows in bold indicate best fitting model in comparison of two mediation sequences; * denotes full mediation model; RMSEA, root mean square error of approximation; CFI, comparative fit index, TLI, Tucker-Lewis Index; AIC, Akaike's Information Criterion; BCC, Brown-Cudeck criteria; χ^2 GOF, Chi square goodness of fit

Table 1 (continued)

	Model (+ baseline)		RMSEA [90% CI]	CFI	TLI	AIC	BIC	χ^2 **GOF**	Indirect effect *p*
Work and Social Adjustment									
Basic Mediation Models	1b	R→A→WSA	0.041 [0, 0.14]	0.997	0.988	1543.5	1597.4	$\chi^2(2)=2.49$, p=0.287	.001
	2b	R→C→WSA	0.034 [0, 0.17]	0.998	0.993	1393.3	1447.2	$\chi^2(2)=2.34$, p=0.311	.001
	3b	R→AB→WSA	0 [0, 0.10]	1.0	1.04	1542.2	1596.1	$\chi^2(2)=0.46$, p=0.793	.09
	4b	R→ SB→WSA	0 [0, 0.07]	1.0	1.05	1567.1	1621.0	$\chi^2(2)=0.22$, p=0.898	.004
Sequential Mediation Models	5b	R→C→A→WSA*	0.151 [0.10, 0.21]	0.929	0.822	1974.8	2061.8	$\chi^2(5)=26.20$, p<0.001	.002
	6b	R→A→C→WSA *	0.160 [0.10, 0.22]	0.911	0.777	2018.6	2105.5	$\chi^2(6)=28.63$, p<0.001	.003
	7b	R→SB→A→WSA *	0.096 [0.03, 0.16]	0.966	0.914	2146.3	2233.2	$\chi^2(6)=14.18$, p=0.028	.025
	8b	R→A→SB→WSA*	0.115 [0.06, 0.18]	0.954	0.884	2125.8	2212.7	$\chi^2(6)=17.66$, p=0.007	.017

Table 2: Direct, Indirect & Total Effects in all models

Symptom Severity			Work and social adjustment		
	b (95% CI)	p		b (95% CI)	p
R →anxiety →SS			**R →anxiety →WSA**		
Group → Anxiety	-.60 (-.90,-.30)	<0.001	Group → Anxiety	-.61 (-.91, -.31)	<0.001
Anxiety → SS	.44 (.25, .62)	<0.001	Anxiety → WSA	.57 (.41,.73)	<0.001
Group → SS	-.04 (-.33, .67)	0.79	Group → WSA	-.19 (-.44, .11)	.18
Group→ Anxiety → SS	-.13 (-.46, -.11)	.002	Group→ Anxiety → WSA	-.35 (-.56, -16)	.001
R →cognitions →SS			**R →cognitions →WSA**		
Group → Cognitions	-.53 (-.79, -.26)	<0.001	Group → Cognitions	-.55 (-.80,-.29)	<0.001
Cognitions → SS	.45 (.23,.66)	<0.001	Cognitions → WSA	.65 (.49, .80)	<0.001
Group → SS	-.08 (-.37, .23)	.62	Group → WSA	-.16 (-.42, .12)	.24
Group→ Cognitions→SS	-.24 (-.43, -.09)	.005	Group→ Cognitions → WSA	-.36 (-.57, -17)	.001
R →avoidance behaviours →SS			**R →avoidance behaviours →WSA**		
Group → Avoidance behaviour	-.49 (-.73, -.23)	<0.001	Group → Avoidance behaviour	-.50 (-.76, -.26)	<0.001
Avoidance behaviour→SS	.22 (-.05, .51)	.13	Avoidance behaviour → WSA	.25 (.02, .47)	.03
Group→SS	.02 (-.36, .41)	.92	Group → WSA	-.23 (-.54, 08)	.14
Group→ Avoidance behaviour →SS	-.11 (-.29, .02)	.19	Group→ Avoidance behaviour →WSA	-.12 (-.30, -..01)	.09
R →safety behaviours →SS			**R →safety behaviours →WSA**		
Group → Safety behaviour	-.96 (-1.24,-.69)	<0.001	Group → Safety behaviour	-.99 (-1.26, -.71)	<0.001
Safety behaviour → SS	.34 (.13, .54)	.001	Safety behaviour → WSA	.35 (.15, .56)	.001
Group →→ SS	.23 (-.14, .58)	.22	Group → WSA	-.03 (-.35, .32)	.86
Group→→ Safety behaviour → SS	-.33 (-.57, -.11)	.005	Group→ Safety behaviour → WSA	-.35 (-.60, -.14)	.004
R →cognitions →anxiety→ SS			**R →cognitions →anxiety →WSA**		
Group → Cognitions	-.51 (-.77, -.25)	<0.001	Group → Cognitions	-.53 (-.79, -.27)	<0.001
Cognitions →Anxiety	.71 (.57, .85)	<0.001	Cognitions →Anxiety	.74 (.58, .88)	<0.001
Anxiety→ SS	.59 (.41, .79)	<0.001	Anxiety→ WSA	.65 (.50, .80)	<0.001
Group→Cognitions→Anxiety→ SS	-.21 (-.38, -.09)	.005	Group → Cognitions→Anxiety→ WSA	-.26 (-.44, -11)	.002

Table 2 (continued)

Symptom Severity			Work and social adjustment		
	b (95% CI)	p		b (95% CI)	p
R→safety behaviours →anxiety→ SS			**R→safety behaviours →anxiety→ →WSA**		
Group→Safety behaviour	-.96 (-1.24, -.68)	<0.001	Group→Safety behaviour	-.99 (-1.27, -.70)	<0.001
Safety behaviour→Anxiety	.34 (.21, .46)	<0.001	Safety behaviour→Anxiety	.33 (.20, .45)	<0.001
Anxiety→SS	.34 (.05, .61)	.015	Anxiety→WSA	.35 (.13, .58)	0.002
Group→Safety Behaviour→Anxiety→ SS	-.11 (-.24, -.01)	.049	Group →Safety Behaviour Anxiety→WSA	-.12 (-.23, -.03)	.025

R. randomisation; A, general anxiety; C, GI related cognitions; SB, GI safety behaviours; WSA, work and social adjustment; SS, symptom severity

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Supplementary Material

Appendix A

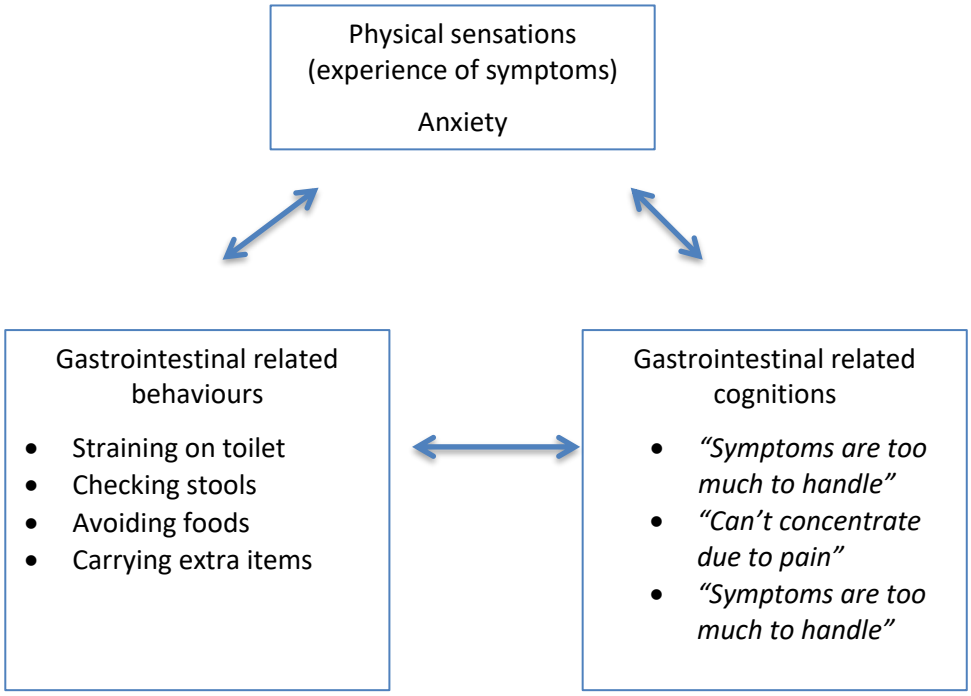

Figure of Three Systems Model in IBS

Appendix B

CBT protocol

Psycho-education provided information about the physiology of the bowel and the brain-gut connection. Cognitive restructuring was aimed at making individuals aware of unhelpful GI-related thoughts, recognising how these affected their behaviours, and GI symptoms. Patients were encouraged to challenge them. Behavioural techniques involved goal setting to increase helpful behaviours such as eating regular meals, whilst reducing unhelpful behaviours. These could be avoidance behaviours such as avoiding situations that may be impacted by bowel symptoms, or safety behaviours such as taking precautionary measures like trying to force the bowels to empty before leaving the house. Techniques to manage stress and prevent relapse were also included. The treatment aimed to improve participants' ability to participate in life despite their IBS symptoms. It was anticipated that IBS symptoms may also reduce.

Appendix C

Measures

The Symptom Severity Scale (SSS) sensitive to change over time (Francis, Morris, & Whorwell, 1997) measures symptom severity specific to IBS. The maximum score is 500, with scores <75 indicating normal bowel function. Scores between 75-174 indicate mild IBS, 175-299 moderate IBS and scores between 300-500 indicate severe IBS. The scale has been shown to have good reliability and validity (Francis et al., 1997).

The Work and Social Adjustment Scale (WSAS) is a measure of work and social functioning. It contains 5 items each rated 0 - 8, with a total potential score of 40. The items assess individuals' ability to engage in day-to-day tasks at work, at home, socially, with family and in relationships. It was found to be a reliable and valid measure of impaired functioning (Mundt, Marks, Shear, & Greist, 2002).

Mediators

The Cognitive Scale for Functional Bowel Disorders (CSFBD) contains items that assess thoughts specific to the experience of functional bowel disorders such as "*my bowel symptoms make me feel out of safety*". The scale consists of 25 items, with a possible total score of 25 to 175 with higher scores indicating more illness-related cognitions. The measure has been demonstrated to have good reliability and validity (Toner et al., 1998).

The Hospital Anxiety and Depression Scale (HADS) contains two subscales measuring anxiety and depression. The present study only used the anxiety subscale of the HADS, which is made up of 7 items scored from 0 to 3, with a total possible score of 21. Scores of 8 and above are said to indicate anxiety (Bjelland, Dahl, Haug, & Neckelmann, 2002) with good sensitivity (0.9). The measure assesses general anxiety rather than anxiety specific to IBS, with items such as "*I feel tense or wound up*".

The IBS Behavioural Responses Questionnaire (IBS-BRQ) consists of two subscales. The first measures avoidance behaviour such as "*I avoid going out in case I have problems with my IBS*" (15 items). The second subscale assesses safety behaviours (11 items), which are referred to as 'safety behaviours' in the scale. An example safety behaviour item is "*I spend more time on the toilet than I would ideally like*". Each item is scored on a scale of 1-7, and the two subscales are scored by summing the total of the items. Higher scores indicate higher levels of unhelpful behaviours. The scale has been shown to have good reliability and validity (Reme, Darnley, Kennedy, & Chalder, 2010).

Appendix D

Methodology regarding selection of partial versus full mediation models

Partial versus full mediation

In mediation the total effect of an independent variable (e.g. treatment) on an outcome can be partitioned into the direct effect (path R to O, figure 1) and the indirect effect (paths from R to O via M, figure 1). The indirect effect quantifies the extent to which the treatment effect on the outcome is transmitted via the mediator (mediated effect). The direct effect quantifies the remaining direct effect of treatment on the outcome. We use the term full mediation model to describe a model explicitly assuming the direct effect is essentially equal to zero, allowing for no direct pathway between treatment and outcome, and so postulate that the full effect of the outcome is transmitted via the mediating variable (full mediation model, figure 1). Models we describe as partial mediation models allow for both direct and indirect pathways (models 1-4 and the partial mediation model, figure 1). In this latter type of model, we can assess whether mediation is partial or full; if there is full mediation, the mediated effect will be statistically significant, with a non-significant direct effect. If the mediated and direct effects are statistically significant, this indicates partial mediation.

The first four models assessed mediation via a single mediator (figure 1). In figure 1, full and partial sequential mediation models are illustrated. Each sequence (e.g. R →GI related cognitions →anxiety→outcome) was tested in the context of a partial mediation model and a full mediation model, and the best fitting model was assessed using the AIC and BIC criteria. This followed the process of the previous mediation paper (Reme, Stahl et al, 2011; Kennedy, Jones et al. 2005) and was used to determine whether the inclusion of a direct path from randomisation to outcome enhanced or detracted from the fit of the models to the data. Once a full or partial mediation model was selected, each sequence was compared using the model fit indices described above. The mediated effect of all models assessed calculated confidence intervals using bootstrap resampling with 1000 repetitions and 95% confidence interval (Chalder, Goldsmith, White, Sharpe, & Pickles, 2015; Efron & Tibshirani, 1994; Shrout & Bolger, 2002; Williams & MacKinnon, 2008).

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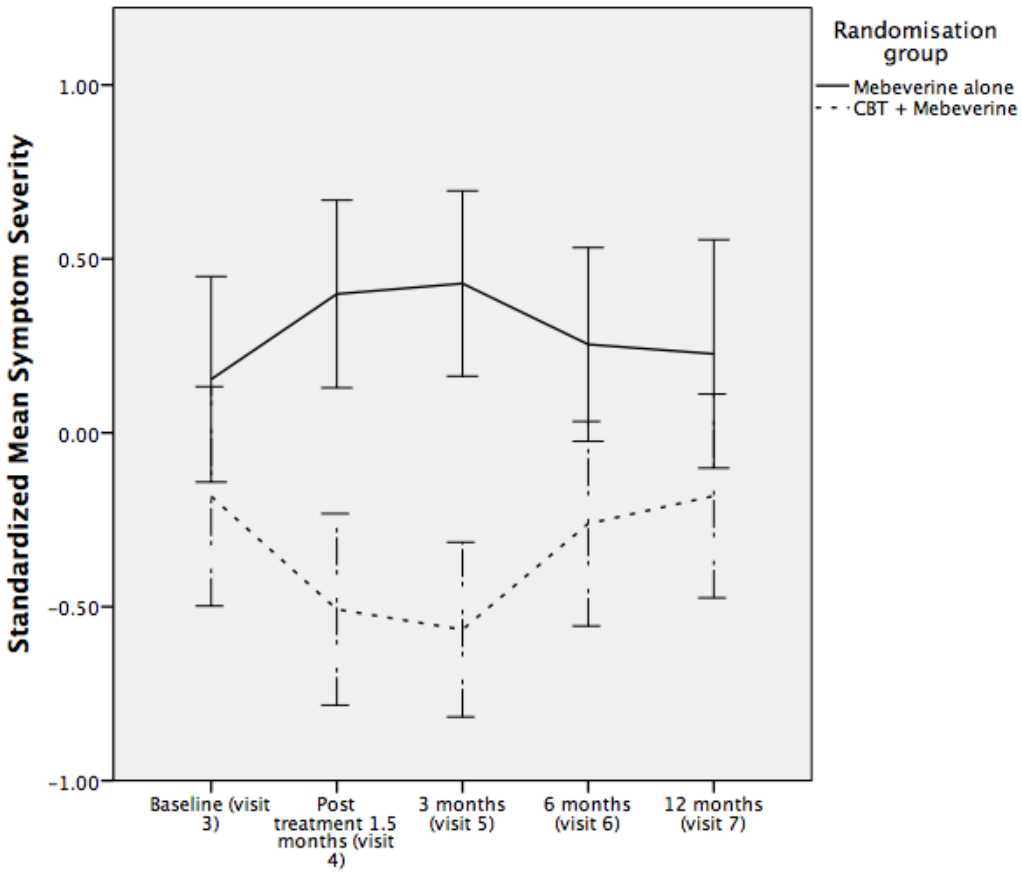
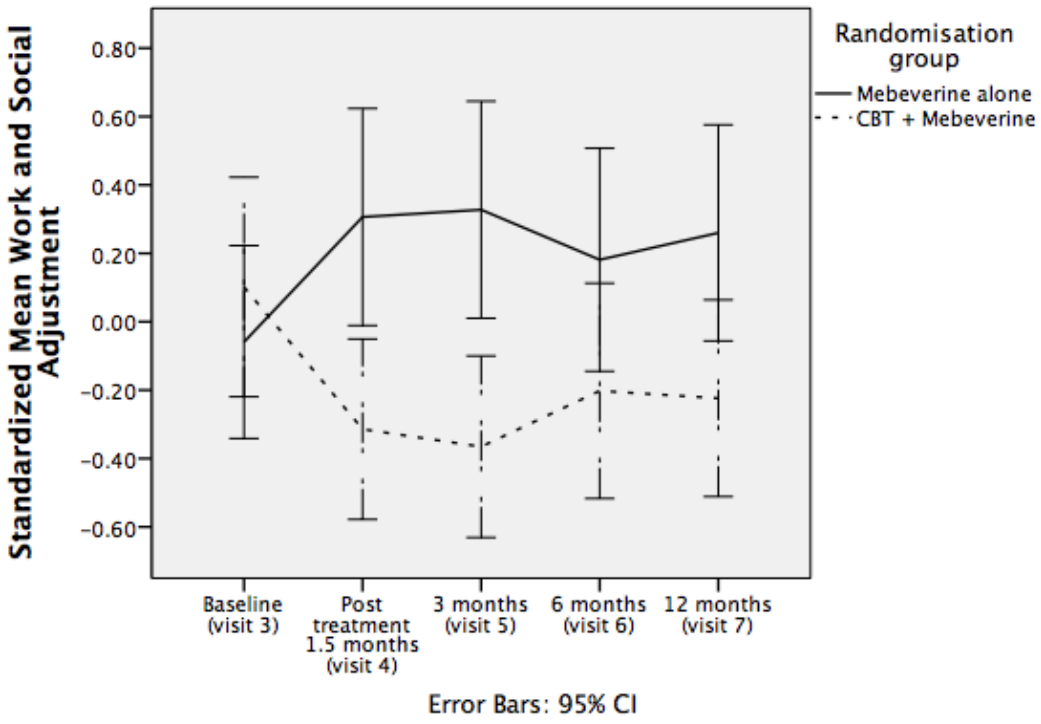
Appendix E:



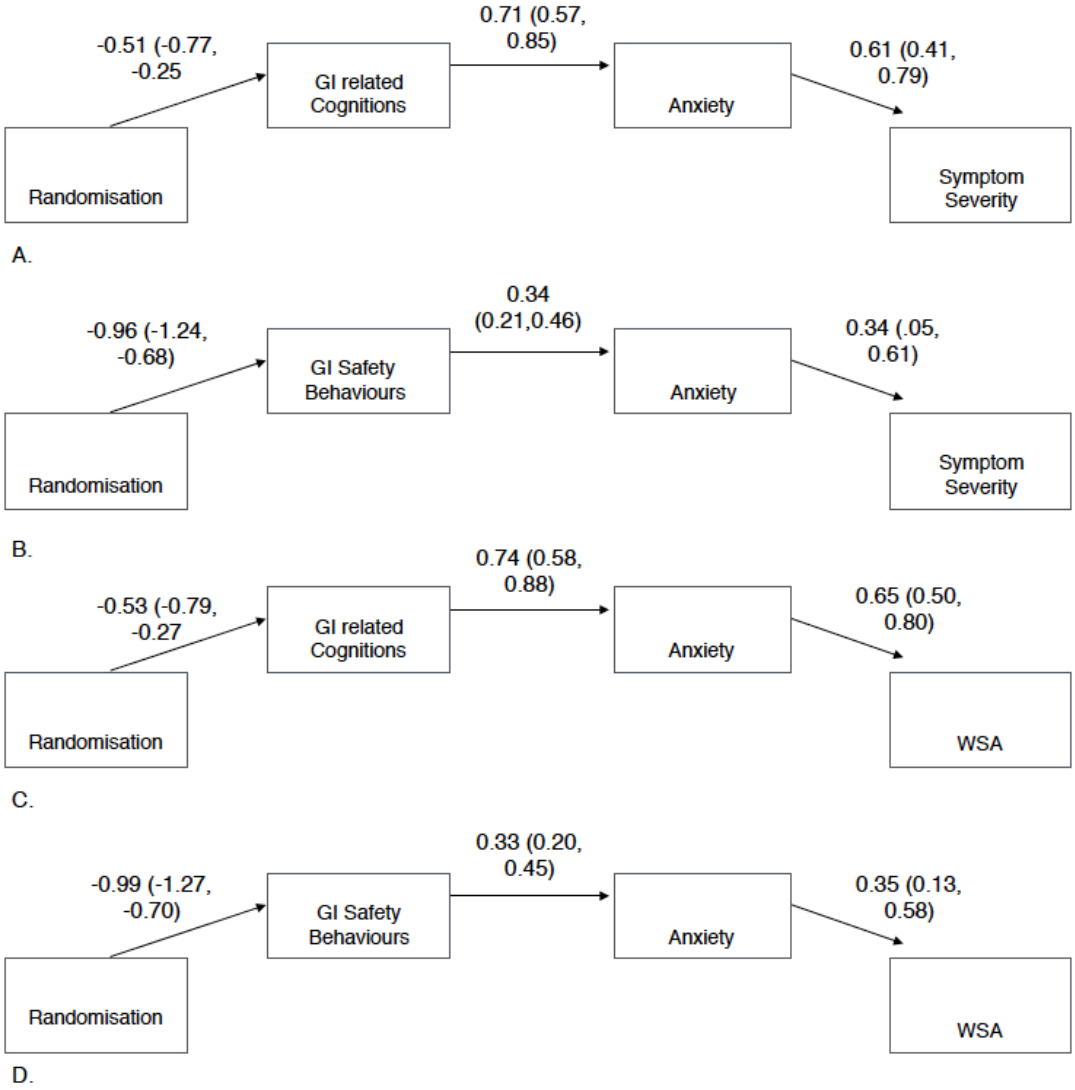
A



B

Trajectory of primary outcomes

Appendix F



Best fitting models as indicated by standardised indirect effect size for symptom severity and work and social adjustment (WSA). Single headed arrows indicate hypothesized relationships between variables with standardized regression coefficients next to each path with 95% confidence intervals in brackets. Not shown in the diagrams for simplicity are the paths indicating the baseline outcome and mediator variables controlled for by including these as predictors for each dependent variable included in the model.

Appendix G: Comparison of model fit indices for full versus partial mediation models of sequences

	Full/Partial Model	RMSEA [90% CI]	CFI	TLI	AIC	BIC	χ^2 **GOF**	Indirect effect *p*
Symptom Severity								
R→C→A→SS	Full	0.070 [0, 0.14]	0.981	0.952	2111.6	2198.5	$\boldsymbol{\chi^2}$**(6)=10.38, p=0.109**	.006
	Partial	0.083 [0, 0.16]	0.977	0.932	2113.3	2203.2	$\chi^2(5)=10.15$, p=0.071	.006
R→A→C→SS	Full	0.102 [0, 0.17]	0.949	0.872	2174.0	2260.9	$\chi^2(6)= 15.20$, p=0.019	.010
	Partial	0.117 [0.05, 0.19]	0.944	0.831	2176.0	2266.0	$\chi^2(5)=15.16$, p=0.010	010
R→SB→A→SS	Full	0.08 [0, 0.15]	0.976	0.939	2218.9	2305.8	$\boldsymbol{\chi^2}$**(6)= 11.17, p=0.083**	.046
	Partial	0.09 [0, 0.16]	0.975	0.924	2220.1	2310.0	$\chi^2(5)=10.42$, p=0.064	.046
R→A→SB→SS	Full	0.121 [0.06, 0.18]	0.943	0.898	2202.0	2289.0	$\chi^2(6)= 18.91$, p=0.004	.014
	Partial	0.119 [0.05, 0.19]	0.954	0.862	2200.6	2290.5	$\chi^2(6)= 15.14$, p=0.009	.014
Work and Social Adjustment								
R→C→A→WSA	Full	0.151 [0.10, 0.21]	0.929	0.822	1974.8	2061.8	$\boldsymbol{\chi^2}$**(6)=26.20, p<0.001**	.002
	Partial	0.166 [0.11, 0.23]	0.928	0.785	1976.0	2065.9	$\chi^2(5)=25.33$, p<0.001	.002
R→A→C→WSA	Full	0.160 [0.10, 0.22]	0.911	0.777	2018.6	2105.5	$\chi^2(6)=28.63$, p<0.001	.003
	Partial	0.177 [0.12, 0.24]	0.908	0.724	2020.2	2110.2	$\chi^2(5)=28.29$, p<0.001	.003
R→SB→A→WSA	Full	0.096 [0.03, 0.16]	0.966	0.914	2146.3	2233.2	$\boldsymbol{\chi^2}$**(6)=14.18, p=0.028**	.025
	Partial	0.105 [0.04, 0.18]	0.966	0.898	2147.2	2237.2	$\chi^2(5)=13.10$, p=0.023	.025
R→A→SB→WSA	Full	0.115 [0.06, 0.18]	0.954	0.884	2125.8	2212.7	$\chi^2(6)=17.66$, p=0.007	.017
	Partial	0.131 [0.07, 0.20]	0.950	0.849	2127.8	2217.7	$\chi^2(6)=17.66$, p=0.003	.017

Rows in bold indicate best fitting model; RMSEA, root mean square error of approximation; CFI, comparative fit index, TLI, Tucker-Lewis Index; AIC, Akaike's Information Criterion; BCC, Brown-Cudeck criteria; χ^2 GOF, Chi square goodness of fit. R. randomisation; A, general anxiety; C, GI related cognitions; SB, GI safety behaviours; WSA, work and social adjustment; SS, symptom severity

Baseline measures of data set 1

Baseline measures taken at visit 1 (n=235)

Variable	Total sample (n=235)	
	Mean	**Standard deviation**
Symptom severity	298.2	94.7
Work and social adjustment	14.3	8.1
GI related cognitions	108.4	30.6
GI related safety behaviours	44.7	10.7
GI related avoidance behaviours	44.5	17.5
Anxiety	11.0	4.6
Depression	7.2	3.8

Baseline Measures taken at visit 3 (n=180)

	CBT + mebeverine (n=89)		**Mebeverine alone (n=91)**		**Total sample (n=180)**	
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard deviation**
Symptom severity	253.5	109.9	272	116.9	262.9	113.6
Work and social adjustment	13.4	8.9	14.5	9.0	14.0	8.9
GI related cognitions	107.2	26.1	109.1	29.8	108.2	28.0
GI related safety behaviours*	44.8	11.3	45.5	10.1	45.2	10.7
GI related avoidance behaviours*	45.3	16.6	45.8	18.0	45.6	17.3
Anxiety	9.6	4.3	10.3	4.9	9.9	4.6
Depression	6.4	3.1	6.7	3.4	6.6	3.3

*measures taken from visit 1

5.3 Summary

The results of this study support the findings from the systematic review in study one (chapter four), that change in GI related cognitions significantly mediate the treatment effect on the outcomes of symptom severity and work and social adjustment (WSA). The results of the systematic review suggested that reducing general anxiety may not be as important for producing change in outcome as changing cognitions. However the results of study two indicated that general anxiety was a significant mediator of treatment effect on both symptom severity and WSA. The systematic review indicated that GSA may be a more important mediator, however because data set 1 was already collected, GSA was not able to be included in the mediation analysis as this had not been measured at the time of data collection. The results of study two, however, may still support the findings of study one with regards to general anxiety being of less, or rather, secondary importance to changing GI related cognitions. This is because the results of the sequential mediation analysis indicated that CBT changed GI related cognitions prior to general anxiety reducing. This sequence then produced change in symptom severity and WSA. Together these studies may therefore establish that of primary importance in CBT for IBS is to achieve a change in GI related cognitions, which will subsequently result in the reduction of anxiety, symptom severity and increase work and social functioning.

Study one identified that there were few studies assessing the potential mediating role of behaviours in CBT for IBS, despite the fact that these are a key process implicated in the CB models of IBS. Study two contributed to the understanding of how particular behaviours may have differential roles in CBT for IBS. Unlike in the one previous study assessing GI related behaviours as mediators in IBS (Reme et al, 2011), study two divided these behaviours into avoidance and safety behaviours in line with the IBS behavioural responses questionnaire subscales (Reme et al, 2010). The simple mediation models demonstrated that safety behaviours were significant mediators of treatment effect on both outcomes however avoidance behaviours were not. This finding could be due to the sample not being particularly avoidant at baseline (page 169). It may also be due to measurement bias, should the IBS-BRQ not sufficiently measure the avoidance tendencies of individuals with IBS or should the measure not be sensitive to change.

In the sequential mediation models of study two, change in safety behaviours were found to occur prior to reduction in anxiety, as with the sequences including GI related cognitions and anxiety. The results of study two along with the findings of study one would therefore suggest targeting change in GI related cognitions and behaviours is

particularly important for achieving change in outcomes, including anxiety. Future studies should seek to assess the mediating role of GSA in addition to GI related cognitions and behaviours. Ideally mediation models would include a measure of all three variables (or more if behaviours were to be subdivided). This would allow comparison of the quantification of the indirect effects of all mediators, in order to identify whether particular variables have stronger mediating effect than others. Such analysis would ideally be conducted in a large sample with sufficient power and a sustained treatment effect.

6. The Importance of Examining Subgroups in Irritable Bowel Syndrome

6.1 Chapter Overview

The previous two studies have investigated psychological treatment mechanisms in IBS to address objective one of the thesis. The subsequent two studies were designed to address objective two: to identify cognitive and behavioural factors associated with IBS bowel pattern subtypes. In IBS subgroups are currently classified according to predominant bowel subtypes only. There are increasing calls to increase the dimensionality of subgroups in IBS, so that they are characterised by additional factors such as psychological comorbidity (Whitehead et al, 2002) and somatic comorbidity (Reidl et al, 2008) in addition to bowel pattern subtype. There are a number of arguments for increasing the multidimensionality of subgroups in IBS, which are presented in this chapter. It presents "cluster analysis" as a means of statistically identifying subgroups that are multi-factorially characterised. This chapter provides a context for the importance of the analysis conducted in studies three and four (chapters seven and eight).

6.2 Submitted Paper

This is published in the *Journal of Mental Health*.

Article Title: The Importance of Cluster Analysis for Enhancing Clinical Practice: An Example from Irritable Bowel Syndrome

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Conflict of Interest Statement: The authors have no competing interests to report

Keywords: Cluster analysis; subgroups; irritable bowel syndrome; heterogeneity; personalised medicine

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Abstract

In clinical populations substantial heterogeneity exists in patient characteristics, illness severity and treatment responses. Better understanding of such heterogeneity may lead to more effective and efficient treatment by personalising care to better suit patient profiles. In this editorial we argue that the statistical method of cluster analysis is a means by which such heterogeneity can be understood, potentially leading to improved care in mental health services. The method is as yet relatively under-utilised and as such the barriers to its use and implementation are also considered.

The Importance of Cluster Analysis for Enhancing Clinical Practice: An Example from Irritable Bowel Syndrome

Introduction

In clinical populations substantial heterogeneity exists in patient characteristics, illness severity and treatment responses. Better understanding of such heterogeneity may lead to more effective and efficient treatment by personalising care to better suit patient profiles. In this editorial we argue that the statistical method of cluster analysis is a means by which such heterogeneity can be understood, potentially leading to improved care in mental health services. The method is as yet relatively under-utilised and as such the barriers to its use and implementation are also considered.

Cluster analysis is a statistical method that identifies subgroups as defined by multiple characteristics. For example in depression there is heterogeneity in terms of age of onset (e.g. early versus late onset), exposure to life stress (Van den Berg et al., 2001) and severity of depression (e.g. mild, moderate or major depressive disorder) (Merikangas et al., 1994). Cluster analysis could help to identify subgroups within this patient population defined by the characteristics of age, stress exposure and depression severity all together. Use of such analysis could have several benefits including the development of diagnostic criteria, explanations of heterogeneous outcomes and tailoring of treatments (Taylor et al., 2001; Song & Jason, 2005). We use the word ‘subgroup’ to refer to subsets of individuals within a given population that can be described using several characteristics. The use of this term should not be confused with what is traditionally called ‘subgroup analysis’ in the clinical trials literature. Subgroup analysis in that literature refers to quantification of treatment responses in subsets of individuals identifiable by a single characteristic (e.g. a demographic or psychological variable). This may involve analysis within the subgroup of interest, or via simple regression models including interaction terms (moderation analysis) (Assmann et al., 2000). Instead, this paper provides a brief overview of cluster analysis, how it can be used to identify subgroups, the usefulness of such analysis and its potential application to clinical practice. We use some recent results in irritable bowel syndrome to illustrate these points.

Diagnostic utility

Mental and physical health diagnostic criteria are often criticised because they are considered to be too restrictive, too broad or to actually exclude important factors within a given condition (Bentall & Pilgrim, 1999; Wakefield, 2010). In irritable bowel syndrome (IBS) there are four subgroups defined by a single parameter - the predominant bowel pattern. Individuals can either be constipation predominant (IBS-C), diarrhoea predominant (IBS-D), alternating (IBS-A) or unclassified (IBS-U). However, assigning individuals to subgroups based on one parameter may limit the diagnostic utility and clinical relevance. Increasing the multidimensionality of the clinical profile of IBS subgroups could aid healthcare professionals in making positive diagnoses of IBS as opposed to diagnosis by exclusion. Improving clarity and validity of diagnostic criteria would also have the benefit of reducing the cost associated with diagnosis by exclusion, which often involves additional consultations and unnecessary diagnostic procedures. It also has a negative effect on the prognosis and illness trajectories of IBS patients as it leaves them with feelings of uncertainty regarding their condition and can lessen trust in healthcare professionals (Spiegel et al., 2010).

Multidimensionality of IBS clinical profiles has been examined using mixture modelling cluster analysis, which included measures of bowel symptom type (IBS-C, IBS-D, IBS-A), symptom severity, the occurrence of extra-intestinal symptoms, anxiety and depression (Polster et al., 2017). Six subgroups were found, identified by bowel pattern subtype and further subdivided by high or low ratings of comorbidities (somatic and psychological). Whilst supporting the distinctions between bowel patterns, the results indicate that assessments of additional somatic and psychological comorbidities are also important factors in distinguishing IBS subtypes. Furthermore, when the groups were compared on symptom severity and anxiety and depression, high comorbidity groups were found to have significantly higher levels of symptom severity, anxiety and depression than low comorbidity subgroups. Level of comorbidity therefore appears to be an important factor in distinguishing levels of symptom severity and psychological distress in IBS. Increasing the multidimensionality of subgroups in IBS could provide a means of understanding heterogeneity in outcomes that subgrouping by bowel pattern alone cannot.

How can cluster analyses improve treatment approaches?

The more comprehensive characterisation of subgroups provided by cluster analysis can help target treatments more specifically. For example in IBS, cognitive behavioural therapy (CBT) is

the primary recommended treatment approach (Spence & Moss-Morris, 2007; Drossman, 2016). CBT aims to change unhelpful cognitions and behaviours contributing to the maintenance of symptoms. When assessing subgroups in IBS, including a measure of such tendencies to engage in unhelpful cognitive and behavioural patterns along with other empirically directed characteristic measures (such as anxiety and bowel pattern subtype) can inform how the different subgroups may be best targeted by CBT. For example two hypothetical subgroups identified by cluster analysis may be (1) individuals with IBS-D and IBS-A with higher levels of gastrointestinal avoidance behaviour and high levels of general anxiety compared with (2) individuals with IBS-C who have high levels of safety behaviours and gastrointestinal (but not general) anxiety. The characterisations of these groups by the different measures included in the cluster analysis would therefore provide a basis for tailoring treatment for the subgroups. For instance group 1 may benefit from behavioural experiments designed to demonstrate the likelihood of having an accident in public and stress management training to reduce general anxiety. In contrast, group 2 may benefit from cognitive restructuring regarding fears about not passing stools and behavioural exposure techniques to reduce anxiety specific to the experience of gastrointestinal sensations. The efficacy of such tailoring could be tested in an experimental design comparing the conditions and a control group with use of moderation analysis. In the context of randomised controlled trials, moderation analysis including clusters (subgroups) would identify whether there is an interaction between cluster membership (e.g. subgroup) and treatment group. In this example, moderation would determine whether membership of group 1 or 2 would affect treatment response in the different conditions.

Methodological Approaches to the Identification of Subgroups

There are numerous approaches available to researchers intending to identify subgroups that exist under the umbrella term of 'cluster analysis' (Nathan & Langenbucher, 2003). One of the most popular methods is finite mixture modelling, such as latent class analysis (LCA) (Stahl & Sallis, 2012). LCA operates on the assumption that a given dataset includes a mixture of scores from different underlying latent classes (subgroups) (Stahl & Sallis, 2012). The approach deduces information about the underlying distributions of the subgroups by identifying similar patterns of values and assessing the probability that certain cases are members of the identified subgroups (Fraley & Raftery, 1998). The LCA algorithm derives a range of subgroups from the data, and uses a goodness of fit statistic such as the Bayesian Information Criteria (BIC) (Nylund et al., 2007) to identify the optimal number of subgroups that adequately explains the distribution of the data. For example, an LCA may identify one model with 5 subgroups (also

termed clusters or classes) and one with 4 subgroups. It will use the BIC goodness of fit statistic to identify which model best fits the observed data.

This method of identifying the optimal number of subgroups is a key advantage of LCA compared to other methods of cluster analysis such as distance based cluster analysis that use more arbitrary criterion. Other advantages of LCA include its ability to combine both continuous and categorical measures to define subgroups and allow for the inclusion of covariates and modelling of directional relationships. This means LCA can control for potential effects of other background variables and when used in prospective data, can be used to assess directional relationships (e.g. whether cluster membership predicts outcome) (Hagenaars & McCutcheon, 2002; Stahl & Sallis, 2012).

Barriers to Implementation

Although cluster methods provide a powerful tool for understanding subgroups and differences in treatment response they also require careful consideration prior to implementation. Good statistical power is necessary for robust results (Lanza & Rhoades, 2013). Sample size depends on the number of clusters being identified and the number of items/variables entered into the analysis (Dziak et al., 2014). There is no consensus on an adequate sample size, but previous research suggests samples above 200 are necessary to achieve sufficient power (Tekle et al., 2016), with some suggesting a minimum sample of 500 (Finch & Bronk, 2011). A strong empirical and/or theoretically informed basis for such analysis is vital to inform which measures are included in analysis and the extent to which clusters identified make theoretical/clinical sense (Breckenridge, 1989). Replication is also essential as the models derived from the analysis use the existing data distribution so further samples are needed to test the robustness of the models (Milligan, 1996). It is therefore recommended that two datasets are used or a large enough dataset that allows splitting the data in two samples. One sample is then used as the 'training' dataset and the other is used as a validation sample (Everitt et al., 2001). Only once the identification of subgroups within a given population has been replicated (cross-validated) in multiple samples would there be a strong enough basis for updating existing diagnostic criteria and informing practice.

Conclusion

Cluster analysis is important for understanding the heterogeneity of clinical disorders, particularly those that challenge customary distinctions between physical and psychological

aetiology. Cluster analysis methods can improve diagnostic criteria to provide more comprehensive and clinically meaningful profiles within a condition. In IBS this involves consideration of psychological aspects such as anxiety and in the future a wider approach including cognitive and behavioural factors. Cluster analysis also has the potential to improve our understanding of differential treatment responses in different patient subgroups and to provide more personalised treatment to enhance recovery.

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7. ANOVAs Assessing Psychological, Work and Social Functioning and Symptom Severity Differences Between IBS Subtypes (Study Three)

7.1 Chapter Overview

The previous chapter presented the importance of examining subgroups in IBS. It proposed the use of cluster analysis techniques such as latent class analysis to increase the multidimensionality of subgroups in IBS. An important first step before conducting such analysis is to identify theoretically and empirically informed variables that should be included in such analysis. The analyses conducted in study three (this chapter) and four (chapter eight) can serve as this first step. The analyses were designed to meet objective two: to identify cognitive and behavioural factors associated with IBS bowel pattern subtypes. Specifically the aim of study three was to assess whether there were differences in cognitive and behavioural factors in addition to levels of anxiety, depression, symptom severity, abdominal pain and work and social adjustment across IBS subtypes. Assessing whether there are psychological and physiological differences between the existing subtypes in IBS can indicate which variables may be important to include in future cluster analysis. It can also help to identify whether the distinctions in bowel pattern predominance are clinically meaningful in the context of psychological interventions for IBS.

One-way ANOVAs were conducted using baseline data (n=235) of individuals diagnosed with IBS and meeting the Rome I criteria (data set 1). Bowel pattern subtype was classified according to the use of the illness perception questionnaire adapted for IBS, which asked participants to rate the frequency of symptoms of diarrhoea and constipation. The results are presented and discussed with consideration of their clinical implications and future study directions.

7.2 Submitted Paper

This chapter is under peer review in *Behavioural and Cognitive Psychotherapy*.

Article Title: Behavioural differences between Irritable Bowel Syndrome subtypes & other psychological associations

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Behavioural differences between Irritable Bowel Syndrome subtypes & other psychological associations

Abstract

Background

Irritable Bowel Syndrome (IBS) is a heterogeneous functional gastrointestinal condition consisting of four subtypes characterised by predominant bowel pattern. Cognitive behavioural therapy is an evidenced based approach formulated to reduce symptom severity and impact on functioning in IBS.

Aims

Our paper aimed to assess the associations between bowel pattern subtypes and a range of psychological factors as well as impact measures.

Method

Three bowel pattern subtypes, diarrhoea predominant (IBS-D), constipation predominant (IBS-C) and alternating bowel pattern (IBS-A) were assessed for associations with psychological variables using one-way ANOVAS. The fourth unclassified bowel pattern subtype (IBS-U) was not compared due to a disproportionately small sample. Variables assessed included functional gastrointestinal specific cognitions, avoidance behaviour, control behaviour, anxiety and depression and abdominal pain.

Results

Individuals with IBS-A had the highest ratings of abdominal pain severity, which were significantly higher than individuals with IBS-D. Those with IBS-A and IBS-D engaged more in unhelpful behaviours than those with IBS-C. IBS-A had higher levels of avoidant behaviour than IBS-C, and had

higher levels of control behaviour than IBS-C and IBS-D. Those with IBS-D showed a non-significant trend towards higher ratings of unhelpful gastrointestinal related cognitions. Unhelpful illness-related behaviour is more prominent in those with IBS-A and IBS-D.

Conclusions

Treatments targeting behavioural techniques in IBS may be particularly helpful to these specific IBS subtypes. The paper identifies specific behavioural techniques relevant to IBS subtypes.

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, with a biopsychosocial aetiology (Drossman, 2016; Lackner, Mesmer, Morley, Dowzer, & Hamilton, 2004). The ROME IV is the most recent diagnostic criteria for IBS, stipulating that a diagnosis of IBS is contingent on the presence of abdominal pain, which must be associated with changes in bowel movements or stool consistency (Drossman, 2016). Symptoms must be experienced for a minimum of once a week consistently for at least six months. There is substantial heterogeneity within IBS, as symptom severity can vary substantially from individual to individual, as can predominant symptom type (Guilera, Balboa, & Mearin, 2005).

The iterations of the ROME criteria have led to different approaches in the categorisation of IBS bowel pattern subtypes. Initially individuals were classified only as being either diarrhoea predominant (IBS-D) or constipation predominant (IBS-C). ROME III (Drossman, 2006) introduced two additional subtypes: (1) Alternating bowel pattern (IBS-A) which includes individuals who frequently experience both constipation and diarrhoea, and (2) Unclassified bowel pattern (IBS-U) where individuals do not regularly experience either type of bowel symptom.

The ROME III criteria specify that classification of bowel pattern subtypes is dependent on the proportion of total stools that are loose/watery or hard/lumpy. The specified scale for assessing this is included in the ROME III criteria (see table 1). A limitation of this scale is that individuals with IBS can experience extensive periods of time without symptomatic stools. Consequently, individuals with IBS could be misclassified. Therefore, a significant change made in the ROME IV criteria is the specification that IBS subtypes should be based on symptomatic stools rather than all stools. Furthermore, the updated criteria consider bowel pattern subtypes to exist on a continuum, rather than as distinct disorders (Drossman, 2016). This acknowledges that bowel pattern subtypes may be transitory rather than stable (Penny et al., 2008) and that symptomatic treatment may consequently vary across consultations.

In addition to the ROME criteria, there are alternative IBS diagnostic tools such as the Manning Criteria (Talley et al., 1990). Research investigating IBS subtypes have inconsistently classified subtypes using differing criteria, or have developed additional tools to identify bowel pattern subtypes such as symptom diaries (Dang, Ardila-Hani,

Amichai, Chua, & Pimentel, 2012; Ersryd, Posserud, Abrahamsson, & Simrén, 2007; Saito et al., 2000; Whitehead and Drossman, 2010). Different approaches to classification of bowel pattern subtypes may be partly responsible for inconsistent findings in research investigating associations between bowel pattern subtypes and psychological and physical factors. Outcomes assessed for associations with subtypes include: (a) symptom severity (Fond et al., 2014), (b) QoL (Dang, et al., 2012; Eriksson, Andren, Eriksson, & Kurlberg, 2008; Jamali et al., 2012; Monnikes, 2011; Simren, Abrahamsson, Svedlund, & Bjornsson, 2001), (c) personality factors (Farnam, Somi, Sarami, Farhang, & Yasrebinia, 2007), (d) demographic factors (Lovell and Ford, 2012a), (e) cognitive factors (Guthrie et al., 2003; Stengel et al., 2010; Sugaya and Nomura, 2008), and (f) anxiety or depression (Eriksson, et al., 2008; Farnam, et al., 2007; Fond, et al., 2014; Sugaya and Nomura, 2008).

In relation to QoL some studies found no difference in QoL between bowel pattern subtypes (Fond, et al., 2014; Guthrie, et al., 2003; Jamali, et al., 2012). In one study worse QoL was found in IBS-A and D compared to IBS-C (Dang, et al., 2012), whereas another study found worse QoL in patients with IBS-C compared to IBS-D (Eriksson, et al., 2008). Similar contradictory findings have emerged when examining the relationship between psychological distress and bowel pattern subtypes. Some indicated that higher levels of anxiety were found in IBS-D compared to IBS-C (Prior, Maxton, & Whorwell, 1990; Sugaya and Nomura, 2008) while others found higher levels of anxiety in IBS-C (Farnam, et al., 2007; Prior, et al., 1990). When examining differences in illness-related cognitions (such as thoughts about symptoms and catastrophising) across bowel subtypes no significant differences were found (Guthrie, et al., 2003; Stengel, et al., 2010; Sugaya and Nomura, 2008). It is important however, to note that studies investigating cognitive differences used different measures of illness-related cognitions and had a variety of methodological problems. These include small sample sizes (Stengel, et al., 2010), unstandardised classification of bowel subtype using symptom diaries (Guthrie, et al., 2003) and failure to include third and/or fourth bowel subtype groups in comparison (Sugaya and Nomura, 2008).

These contradictory findings are indicative of a need for better understanding of psychological factors potentially associated with the different IBS subtypes. Formulating a clearer picture of such factors could enhance the design and development of psychological treatment approaches for IBS. Treatments such as Cognitive Behavioural Therapy (CBT) have established efficacy in improving quality of life (QoL) and

symptom severity in IBS (Ford, Talley, Schoenfeld, Quigley, & Moayyedi, 2009; Lackner, et al., 2004). In a mediation study of CBT in IBS, it was found that gastrointestinal specific cognitions and behaviours were mediators of change in both of the outcomes of work and social adjustment and symptom severity (Reme et al., 2011). These results demonstrate the importance of cognitive and behavioural factors in IBS. Therefore, increasing understanding in how these factors relate specifically to bowel subtypes could lead to therapeutic techniques being tailored to the particular bowel symptoms experienced by individuals. This would be particularly useful when tailoring interventions and when designing online and remote IBS interventions.

Some researchers have questioned the clinical value of sub-classification in IBS based on predominant bowel patterns (Guthrie, et al., 2003; Heitkemper et al., 2011). Indeed a previous study investigating the psychological differences across IBS subtypes, subdivided the bowel pattern subtypes further according to whether individuals classified under each bowel pattern, also experienced either high or low abdominal pain (Heitkemper, et al., 2011). They then investigated whether the interaction between bowel pattern subtype and abdominal pain classification was associated with a range of physical and psychological outcomes. These outcomes included QoL, symptom severity, IBS-specific cognitions and anxiety, which were found to significantly differ between abdominal pain categories (high or low) but not bowel pattern subtypes. One significant interaction was found whereby those with IBS-A and IBS-D who also had high abdominal pain, were more likely to have higher symptom severity ratings. This research suggests that abdominal pain, an important factor for the diagnostic criteria of IBS, may also be important in the subtyping of IBS.

The aim of this study was to further investigate the characterisation of bowel pattern subtypes in several ways. We replicated previous studies in testing the associations of subtypes with physical and psychological outcomes but with the addition of unhelpful IBS-specific behaviours as a potential distinguishing factor. These are identified as important factors in maintaining symptoms in IBS according the cognitive behavioural models of IBS (Kennedy et al., 2005) and have been found to influence cognitive change in the context of cognitive behavioural treatment (Reme, et al., 2011). Specifically, we sought to understand whether unhelpful gastrointestinal specific cognitions and behaviours were differentially associated with bowel pattern subtypes in IBS. We hypothesised that due to the nature of the symptoms and the additional burden they create, IBS-A and IBS-D subtypes would be associated with more extreme

symptoms, disability and cognitive behavioural responses as compared to IBS-C. This is because both subtypes experience diarrhoea, which is likely to be more unpredictable and cause more acute inconvenience and uncertainty than the symptom of constipation. As such individuals may have more concerns about public embarrassment than those with IBS-C. IBS-A has also been of particular empirical interest due to its heterogeneity and has previously been found to be associated with increased physical and psychological symptoms (Fond, et al., 2014; Jamali, et al., 2012; Singh et al., 2014). In addition, building on previous research by Heitkemper et al (2011) we aimed to assess whether abdominal pain was associated with particular bowel pattern subtypes.

Table 1: ROME III classifications of IBS bowel subtypes

	Stool Type	
Bowel Subtype	**Loose/Watery**	**Hard/Lumpy**
IBS-D	>25%	<25%
IBS-C	<25%	>25%
IBS-A	>25%	>25%
IBS-U	<25%	<25%

Method

The present study used the baseline data previously collected in a study assessing the efficacy of CBT in addition to antispasmodic treatment in IBS (Kennedy et al., 2005). Two hundred and thirty-five individuals aged 16-50 with moderate to severe IBS symptoms were initially recruited from general practices in South London. There were three data collection time points before individuals began treatment: upon referral to the nurse (visit 1), after 2 weeks of GP care (visit 2) and upon randomisation (visit 3). Data used for this secondary analysis were taken from visit 1, prior to randomisation. Ethical approval was received from St Thomas' Hospital Research Ethics Committee, Guy's Hospital Research Ethics Committee and Barnet, Enfield and Haringey LREC.

Measures

Classification of IBS Bowel Pattern Subtypes

Predominant bowel pattern was identified through recoding of the adapted "Illness Identity symptom" items of the Illness Perception Questionnaire (IPQ) (Moss-Morris et al., 2002), which asked participants how often they experienced diarrhoea and constipation. Responses were rated as "never = 0", "occasionally = 1", "frequently = 2" or "all of the time = 3".

Constipation predominant IBS was defined as individuals who never experienced diarrhoea and scored ≥1 for constipation. Diarrhoea predominant was defined as individuals who never experienced constipation and scored ≥1 for diarrhoea. Individuals who scored ≥1 for constipation and diarrhoea were classified as having alternating bowel pattern. Those who scored 0 for both diarrhoea and constipation were excluded from analysis as there were too few to form a meaningful comparison group (n=8).

Abdominal Pain

Abdominal pain was assessed using an item from the Gastrointestinal Rating Scale (Revicki, Wood, Wiklund, & Crawley, 1997). This assessed the severity of abdominal pain on a Likert scale ranging from "no discomfort at all" = 0 to "severe discomfort" = 5.

IBS Symptom Severity Scale (IBS-SSS) (Francis, Morris, & Whorwell, 1997).

The IBS-SSS is a well-validated and reliable measure of symptom severity in IBS (Francis, et al., 1997), consisting of 12 items with a maximum possible score of 500. Mild, moderate and severe cases of IBS are indicated by scores of 75 to 175, 175 to 300 and >300 respectively. Clinically meaningful change has been identified as a score change of ≥50 (Passos et al., 2009).

Work and Social Adjustment Scale (WSAS) (Mundt, Marks, Shear, & Greist, 2002)

The WSAS is a five-item questionnaire measuring ability to participate in five areas of life: social leisure, work, private leisure, relationships and home management. Each item is scored on a scale of 0 – 8, with 0 being not at all impaired and 8 being severe impairment in the given aspect of life. The maximum score is 40. Scores of 10 and above indicate significant functional impairment and scores of 20 and above

indicate severe impairment. It has been demonstrated to have good reliability with Cronbach's α ranging from 0.70 to 0.94, and good validity (Mundt, et al., 2002). The WSAS is sometimes taken as a measure of QoL (Moss-Morris, McAlpine, Didsbury, & Spence, 2010).

Hospital and Anxiety Scale: Anxiety and Depression (HADS) (Zigmond and Snaith, 1983)

The HADs is a well-established measure of anxiety and depression. The scale consists of 14 items, 7 measuring anxiety and 7 measuring depression, all of which are scored from 0 – 3. A total composite score can be calculated ranging from 0 to 42 (Norton, Cosco, Doyle, Done, & Sacker, 2013), as well as individual scores ranging 0 to 21 for anxiety and depression subscales. For the subscale, scores of 0-7 are considered normal, 8-10 mild anxiety/depression, 11-14 moderate anxiety/depression and 15-21 severe anxiety/depression. It has been demonstrated to have good reliability and validity *(Zigmond and Snaith, 1983).*

Cognitive Scale for Functional Bowel Disorders (CS-FBD) (Toner et al., 1998)

The CS-FBD is a measure designed to assess negative illness cognitions in IBS. It consists of 25 items, each rated on a Likert scale 1 to 7, with higher scores indicating more negative IBS-related thoughts. The total score ranges from 25 to 175. It has been demonstrated to have good reliability (α= .93) and validity (Toner, et al., 1998).

The Irritable Bowel Syndrome Behavioural Responses Questionnaire (IBS- BRQ) (Reme, Darnley, Kennedy, & Chalder, 2010)

The IBS-BRQ is a measure of unhelpful behaviours specific to IBS. It has two subscales, one measuring avoidant behaviours (15 items) and one measuring control behaviours (11 items). Example of an avoidant item would be "*I avoid going out in case I have problems with my IBS"* and an example of a control item would be "*After opening my bowels, I check my stools*". Each item is rated on a Likert scale of 1 to 7 with higher scores indicating higher levels of unhelpful behaviours. The scale has been demonstrated to have good reliability and validity (Reme, et al., 2010).

Analyses

Demographic variables, including gender, age, ethnicity, marital status, IBS duration and post infective IBS instances, were summarised across the subtype groups. The difference in age between the groups was assessed using a one-way ANOVA. Differences across subtype groups in the categorical variables of interest: ethnicity grouping, marital status, banding of IBS duration and whether IBS was post-infectious or not, were assessed using Chi Square tests of independence.

One-way ANOVAs were used to examine associations between IBS bowel pattern subtypes and each of the dependent variables (cognitive and behavioural responses, anxiety, depression, pain, symptom severity and work and social adjustment). Although pain was assessed as one item on a Likert scale, it was treated as a continuous variable upon comparisons of the distributions for each subtype, which were assessed as normal. ANOVA assumptions were investigated for all dependent variables. Homogeneity of variances across subtypes was assessed using Levene's test statistic. Where there was homogeneity of variance across subtypes, the F-test statistic was used to assess the overall association between IBS subtype and the dependent variable, with Tukey's Honest Significant Difference (HSD) used to evaluate individual comparisons between the subtypes. Where the assumption of homogeneity of variance was violated, Welch's test statistic and the Games-Howell post hoc test were used.

Results

The division of the bowel symptoms into three categories, IBS-C, IBS-D and IBS-A resulted in 67% of participants being categorised as IBS-A group (n=156), 18% as IBS-D (n= 43) and 12% IBS-C (n= 27). Unclassified (IBS-U) individuals made up 3% (n=8) of the total sample. There were no significant differences in demographics between the groups other than IBS-C having significantly fewer individuals with post-infective IBS (table 2). Although not significantly different, there was a higher proportion of those with IBS-A (38.5%) and IBS-D (37.2%) categorised as single than those with IBS-C (14.8%).

Table 2: Demographics across bowel subtype groups

	IBS-C n = 27	**IBS-D n = 43**	**IBS-A n = 156**	**P value**
Age at time of referral Mean (SD)	34.4 (7.9)	33.2(7.9)	33.6(8.9)	.85
Female gender n (%)	22 (81.5)	33 (76.7)	131(84.0)	.54
Ethnicity n (%)				.12
White	20 (83.4)	34 (85)	120 (82.3)	
Asian	1 (4.2)	2 (5)	2 (1.4)	
Afro/Caribbean	1 (4.2)	2 (5)	18 (12.3)	
Mixed	2(8.3)	2 (5)	3 (2.1)	
Other	0(0)	0 (0)	3 (2.1)	
Marital Status n (%)				.08
Single	4(14.8)	16(37.2)	60(38.5)	
Married/Cohabiting	14(51.9)	16(37.2)	70(44.9)	
Widowed/separated/divorced	9(33.3)	11(25.6)	26(16.7)	
IBS duration n (%)				.44
3 months – 1 year	4(14.8)	9(20.9)	22(14.1)	
1-5 years	13(48.1)	14(32.6)	52(33.3)	
5 years +	10(37.0)	20(46.5)	82(52.6)	
IBS started with gastroenteritis n (%)	26(96.3)	32(74.4)	133(85.3)	.034*

IBS-A: Unhelpful IBS-specific behaviours & symptom severity

Abdominal pain was significantly higher in those with IBS-A compared to those with IBS-D (MD=.8, p=.021, 95% CI .09, 1.4). Those with IBS-A also had the highest mean severity and those with IBS-D had the lowest mean symptom severity, although these differences were not significant (table 4).

A significant difference between subtypes was detected for avoidance behaviours F (2,178) =7.2, p=.001 and control behaviours F (2,178) =9.0, p<.001. Specifically, IBS-A had significantly higher levels of avoidance behaviours than IBS-C (MD= 13.8, p=.004, 95% CI -23.9, -3.8) (figure 1, panel A). IBS-A also had higher levels of control behaviours than IBS-C (MD= 7.2, p=.017, 95% CI 1.1, 13.4) and IBS-D (MD=7.2, p=.001, 95% CI 2.5, 11.9) as depicted in figure 1, panel B.

IBS-D: Avoidance behaviour & unhelpful gastrointestinal-specific cognitions

Those with IBS-D also had significantly higher levels of avoidance than the IBS-C group, (MD= 18.3, p=.001, 95% CI 6.7, 30.0) as shown in figure 1, panel A. There were no significant differences in the level of avoidance behaviours between IBS-D and IBS-A, or in the level of control behaviours between IBS-D and IBS-C (figure 1, panel B).

There was a larger mean difference in unhelpful cognitions between IBS-D and IBS-C, as compared to those between the other subtypes (table 4). However, the differences between the subtypes did not reach statistical significance F(2,192) =1.7, p=.18) (figure 1, panel C).

Comparable outcomes across IBS subtypes

Work and Social Adjustment scores did not significantly differ across the three IBS subtypes F (2,217) =.08, p=.93 (table 3 and 4). There were also no significant differences between subtypes for anxiety F(2,219) =.098, p=.91 or for depression F(2,221) =.045, p=.96. Group means were similar for each subtype for both outcomes also (table 4).

[insert table 3, table 4 and figure 1]

Table 3: Means and standard deviations of outcomes across IBS subtypes

	IBS-C		***IBS-D***		**IBS-A**	
	n = 27		***n = 43***		**n = 155**	
Dependent Variable	***M* (±SD)**	***95% CI***	***M* (±SD)**	***95% CI***	***M* (±SD)**	***95% CI***
Abdominal Pain	2.9 ±1.8	2.2, 3.6	2.8 ±1.8	2.2, 3.3	3.5 ±1.5	3.3, 3.8
Symptom Severity	300 ±104	259, 341	277, ±97	247, 307	309 ±88	295, 322
Work & Social Adjustment	14 ±7	11, 17	14 ±18	12, 17	14 ±8	13, 15
Cognitions	101±27	90, 113	115 ±25	107, 124	108 ±30	103, 114
Avoidance Behaviours	31±14	24, 38	49 ±17	43, 55	45 ±17	42, 48
Control Behaviours	39± 9	34, 44	39 ± 9	36, 42	46 ±10	44, 48
Anxiety	10±4	8, 12	11 ±4	9, 12	11 ±4	10, 11
Depression	7±3	6, 8	7 ±5	5, 8	7 ±3	6, 7

M, Mean; SD, standard deviation; CI, confidence interval

Table 4: *Mean differences in psychological & severity measures between IBS subtypes*

						95% CIs	
	F	P_1	**Group Contrast**	**Mean Difference**	P_2	**Lower Limit**	**Upper Limit**
Abdominal Pain	4.6	.01	IBS-D – IBS-C	-.1		-1.1	.8
			IBS-D – IBS-A	-.7	.02	-1.4	-.1
			IBS-A – IBS-C	.6		-.2	1.4
Symptom Severity	1.9	.14	IBS-D - IBS-C	-23.2		-76.5	30.2
			IBS-D – IBS-A	-31.7		-69.1	5.7
			IBS-A – IBS-C	8.5		-36.8	53.8
Work and Social Functioning	0.08	.93	IBS-D - IBS-C	0.6		-4.2	5.3
			IBS-D – IBS-A	0.5		-2.8	3.8
			IBS-A – IBS-C	0.1		-4.0	4.1
Cognitions	1.7	.12	IBS-D - IBS-C	14.1		-4.1	32.4
			IBS-D – IBS-A	7.0		-5.9	19.9
			IBS-A – IBS-C	7.1		-8.4	22.6
Avoidance	7.1	.001*	IBS-D - IBS-C	18.3	.001*	6.7	30.0
			IBS-D – IBS-A	4.5		-3.2	12.2
			IBS-A – IBS-C	13.8	.004*	3.8	23.9
Control	9.0	>.001*	IBS-D - IBS-C	0.1		-7.1	7.2
			IBS-D – IBS-A	-7.2	.001*	-11.9	-2.5
			IBS-A – IBS-C	7.2	.017*	1.1	13.4
Anxiety	0.1	.91	IBS-D - IBS-C	0.5		-2.2	3.1
			IBS-D – IBS-A	.3		-1.6	2.2
			IBS-A – IBS-C	0.2		-2.0	2.4
Depression	0.05	.96	IBS-D - IBS-C	-.2		-2.4	2.0
			IBS-D – IBS-A	-.0		-1.5	1.6
			IBS-A – IBS-C	-.2		-2.1	1.6

F, F statistic; P_1, significance of one way ANOVA between groups; P_2, significance of one way ANOVA post hoc comparisons; CIs, confidence intervals

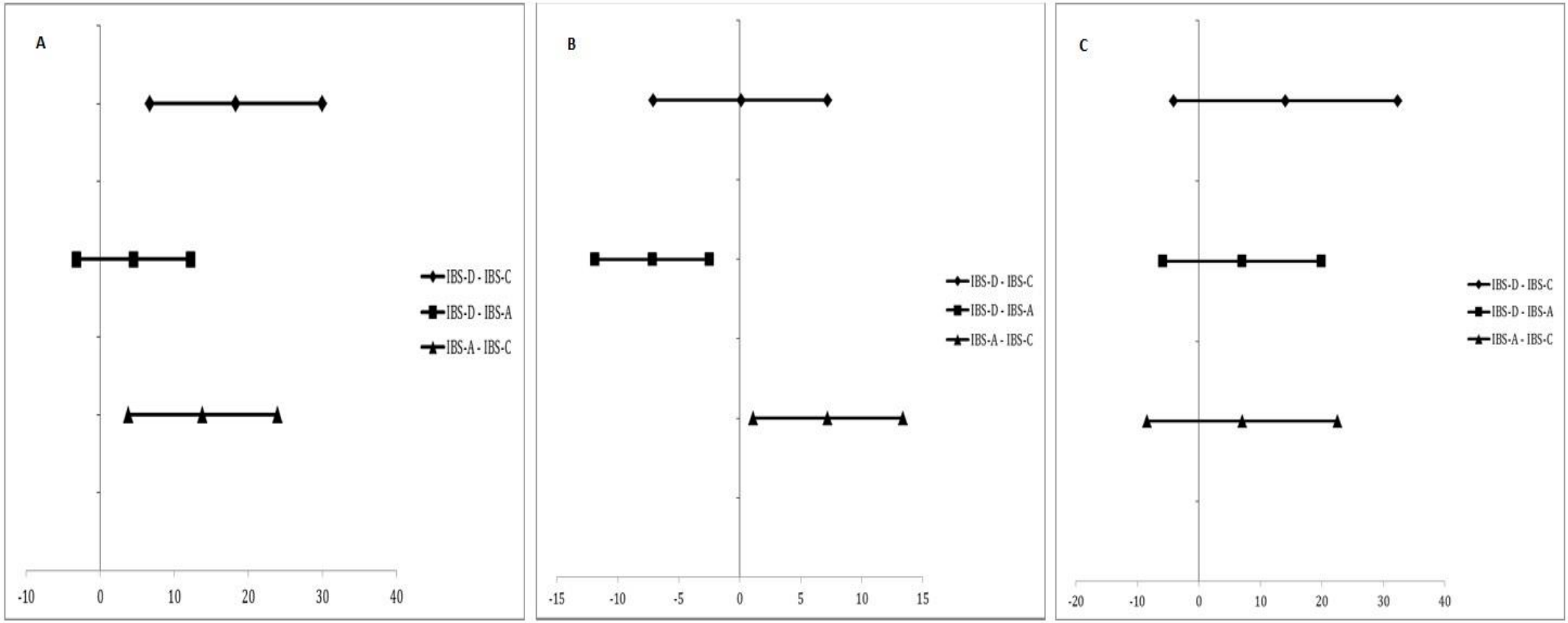

Figure 1: A, Mean differences in avoidance behaviours with upper and lower 95% confidence limits across groups; B, mean differences in control behaviours with upper and lower 95% confidence limits across groups; C, mean differences in gastrointestinal specific cognitions with upper and lower 95% confidence limits across groups

Discussion

The main aim of this paper was to investigate whether bowel symptom subtypes were associated with particular psychological characteristics or varied in the degree of symptom severity, abdominal pain or functioning. The psychological factor distinguishing the IBS subtypes was the degree of unhelpful IBS-specific behaviours. As predicted those with IBS-A engaged in unhelpful behaviours more than those with IBS-C. They were also the group with the highest levels of abdominal pain. Our findings would suggest that across the IBS subtypes, individuals present with similar levels of symptom severity, work and social functioning and distress. These findings are comparable to the findings of previous studies (Drossman et al., 2009; Guthrie, et al., 2003; Jamali, et al., 2012; R Moss-Morris, et al., 2010; Reme, et al., 2011; Rey, Garcia-Alonso, Moreno-Ortega, Alvarez-Sanchez, & Diaz-Rubio, 2008).

Cognitive & Behavioural Differences

Our results suggest that those with IBS-A and IBS-D are prone to more avoidant behaviours relating to their symptoms than those with IBS-C. A qualitative study investigating psychological factors impacting on QoL in IBS found that uncertainty and unpredictability of symptoms were identified as key factors impacting upon cognitive and behavioural reactions to having IBS (Drossman, et al., 2009). Our findings are consistent with this and it makes intuitive sense that individuals with an unpredictable symptom such as diarrhoea might be more prone to control behaviours such as these. In comparison, the symptom of constipation may provide less uncertainty, which may negate excessive control and avoidant behaviours. Individuals with IBS-A also had significantly higher levels of control behaviours than those with IBS-C and IBS-D.

There was an apparent mean difference in unhelpful cognitions between IBS-D and IBS-C subtypes. This difference was not statistically significant which may be due to inadequate power, however it was appreciably larger than the other subtype contrasts. This could indicate a greater tendency towards unhelpful cognitions in those with IBS-D as compared to those with IBS-C. A previous study investigating cognitive differences between subtypes found that cognitive appraisals in the IBS-D group were more extreme compared to controls compared to the IBS-C group (Passos, et al., 2009). The cognitive appraisals were measured using a four-factor scale that assessed the extent that symptoms were perceived as threatening, controllable and affecting their lives and the

extent to which individuals were engaged in trying to address their symptoms. The scale therefore shares qualities with the CS-FBD but the items do differ and load onto four distinct factors, unlike the CS-FBD, which is a unitary scale. Results from these studies suggest that there may be an important distinction in the cognitive tendencies of those with IBS-D compared to those with IBS-C.

Limitations

There are some limitations of our study with respect to measurement. Perhaps the most fundamental limitation is the designation of IBS subtypes.

Classifications of bowel subtypes could not be made in accordance with Rome III or Rome IV criteria as these was not used in the original trial (Kennedy, et al., 2005). Nevertheless, the IPQ items used to create classifications did closely resemble those of the Rome III and if anything, had more explicit wording with regards bowel pattern predominance. Another more salient limitation was that the measurements of bowel patterns were not limited to symptomatic bowel movements only. This was due to the original collection of data predating the Rome IV criteria. The results shown here should be replicated using a sample where the updated classification of bowel pattern subgroups has been applied.

The method used to assess bowel pattern subtypes returned a proportionately low number of individuals with IBS-U compared to other studies (Lovell and Ford, 2012b). This led to this group being excluded from analysis, precluding any insight into the aspects of symptoms, functioning and behaviours in these individuals. Furthermore, the overall sample was relatively small. This compromised the power of the study to detect relationships that may exist in the wider population. Future studies should be designed with larger sample sizes to more rigorously assess these relationships. A meta-analysis reporting on affective differences across IBS subtypes similarly concluded that there is need for future studies with larger sample sizes and greater power in order to resolve inconsistent findings (Fond, et al., 2014).

It should also be noted that the participants took part in a RCT (Kennedy, et al., 2005) assessing the efficacy of CBT in addition to antispasmodic treatment in IBS. As such the results may only be representative of a limited subsection of those with IBS: those that were willing to be enrolled in a clinical trial. There is the possibility that results could also be confounded by self-selection bias (Ford, et al., 2009). The

eligibility criteria of this trial limited inclusion to those with a clinical diagnosis of IBS, meeting Rome I criteria. Participants were excluded if they were pregnant, had co-occurring disease such as inflammatory bowel disease or coeliac or were treating abdominal pain successfully with acid-inhibiting drugs. As such, the present results may not be generalisable to other populations.

Conclusions

The present study is the first to our knowledge that has investigated the potential differences in IBS related behaviours between IBS subtypes. The results may have implications for psychological treatments for IBS. Two of the main targets for change in CBT are avoidance and control behaviour. Our results suggest that targeting avoidance behaviours may be particularly important for IBS-A and IBS-D subtypes. Techniques such as graded exposure to feared stimuli (e.g. leaving the house for increased increments in time when feeling symptoms) can be used to help reduce avoidance. Reductions in control behaviour in IBS-A individuals can be facilitated by goal setting. For example individuals may aim to reduce the number of times they check their stools, or aim to increase the amount of time they are out in public without checking for the nearest toilet. It may therefore be appropriate to tailor behavioural techniques such as according to the IBS subtype presenting. As such it is important for clinicians to ascertain the bowel pattern subtype in the context of psychological assessment and formulation for IBS.

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7.3 Summary

The study identified some key cognitive and behavioural differences between IBS bowel pattern subtypes. Those with IBS-A and IBS-D engaged more in unhelpful behaviours than those with IBS-C. IBS-A had higher levels of avoidant behaviour than IBS-C, and had higher levels of safety (control) behaviour than IBS-C and IBS-D. Those with IBS-D showed a non-significant trend towards higher ratings of unhelpful gastrointestinal related cognitions. Although there were no differences in symptom severity between subtypes, those with IBS-A had significantly higher ratings of abdominal pain severity than the other two subtypes. The results suggest that unhelpful illness-related behaviour is more prominent in those with IBS-A and IBS-D than those with IBS-C. Psychological treatment approaches to IBS, such as CBT, may be modified to focus on the targeting of the particular GI related behaviours associated with these IBS subtypes. The CBT-IE model adapted for IBS (section 1.13.3) may be particularly suited to such subtypes as this focuses on the use of exposure techniques. Distinctions in cognitive and behavioural factors between subtypes may suggest that these are important variables to include in future analysis designed to increase the multidimensionality of subgroups in IBS.

Nevertheless, the analysis was conducted in a sample of participants that met the Rome I criteria, which is now out-dated and replaced with the Rome IV criteria. Studies have shown that the Rome I criteria is less restrictive than the subsequent iterations (Chey et al., 2002; Drossman & Dumitrascu, 2006; Dang et al., 2012) and therefore the same analysis in a sample of participants meeting the Rome III/IV criteria may not demonstrate the same findings. The study was not powered a priori to detect differences between subtypes on all of the outcome variables assessed. As such power to detect differences varied across the dependent variables (appendix G). To validate the findings, it is necessary to replicate the analysis in a greater sample of IBS participants, ideally meeting the Rome III or Rome IV criteria as these share the most updated subtype classification guidelines.

8. ANOVAs Assessing Psychological, Work and Social Functioning and Symptom Severity Differences Between IBS Subtypes (Study Four)

8.1 Chapter Overview

The final study presented in this chapter shared the objective and aims of study three in the previous chapter. The objective was to identify cognitive and behavioural factors associated with IBS bowel pattern subtypes. The aim was to assess whether there were differences in cognitive and behavioural factors in addition to levels of anxiety, depression, symptom severity and work and social adjustment across IBS subtypes. Study four aimed to validate the findings from study three in a larger sample with bigger power to detect differences across the different dependent variables. It was hypothesised that cognitions and behaviours would differ between subtypes. Based on previous results, the three specific hypotheses were that (1) unhelpful cognitions would be greater in those with IBS-D than IBS-C, (2) unhelpful avoidance behaviours would be greater in those with IBS-D and IBS-A compared to IBS-C, and (3) safety (control) behaviours would not significantly differ across subtypes.

Analysis replicating study three, was conducted on baseline data of 557 individuals with refractory IBS recruited into the assessing cognitive therapy in irritable bowel (ACTIB) randomised controlled trial (data set 2). Bowel pattern subtype was classified according to the ROME III criteria.

8.2 Submitted Paper

This chapter is under review in *Behavior Therapy*.

Article Title: Cognitive and behavioural differences between irritable bowel syndrome subtypes

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Keywords: Irritable bowel syndrome; IBS; subtypes; gastrointestinal cognitions; avoidance behaviours; safety behaviours; cognitive behavioural therapy

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Cognitive and behavioural differences between irritable bowel syndrome subtypes

Abstract

Irritable bowel syndrome (IBS) is a functional gastrointestinal syndrome consisting of four bowel pattern subtypes: diarrhoea predominant, (IBS-D) constipation predominant (IBS-C), alternating (IBS-A) or unclassified (IBS-U). This paper aimed to identify whether there were significant associations between bowel pattern subtypes in irritable bowel syndrome and psychological factors or outcome variables. One-way ANOVAs were conducted to assess differences between IBS-related cognitions, behaviours, general anxiety, depression, symptom severity and work and social adjustment. Analysis was conducted on baseline data of 557 individuals with refractory IBS recruited into the assessing cognitive therapy in irritable bowel (ACTIB) randomised controlled trial. Bowel pattern subtype was classified according to the ROME III criteria. Due to the small number of individuals with IBS-U (n=16), this group was excluded from analysis. The most predominant bowel pattern subtype was IBS-A (n=287). IBS-D (n=178) was more predominant than IBS-C (n=76). Results indicated that individuals with IBS-D had significantly higher levels of unhelpful cognitions than those with IBS-C. Those with IBS-D and IBS-A engaged in more unhelpful IBS-related avoidance behaviours than those with IBS-C. In contrast both IBS-C and IBS-A engaged in more unhelpful safety behaviours than those with IBS-D. The results may be important for informing assessment and formulation in psychological therapies for IBS.

Introduction[1]

Irritable bowel syndrome (IBS) is a functional gastrointestinal syndrome characterised by abdominal pain and associated disruptions to bowel patterns. The aetiology of IBS is generally agreed to be of biopsychosocial origin as biological, psychological and social factors interact to cause and maintain IBS symptoms (Drossman, 1996, 2016). Diagnostic criteria have been developed over the years to diagnose IBS in the absence of any physiological markers. The most current diagnostic criteria are the ROME IV criteria (Drossman, 2016). Four IBS subtypes are classified on the basis of the bowel pattern predominance: Constipation predominant (IBS-C), diarrhoea predominant (IBS-D), alternating bowel pattern (IBS-A) or unclassified IBS (IBS-U) for individuals who do not fall into the other bowel pattern categories. The IBS subtypes are thought to be reflective of differential pathophysiological mechanisms that may be targeted by pharmacotherapeutic approaches (Krogsgaard, Engsbro, & Bytzer, 2013). As yet it is unclear as to whether differentiation in bowel pattern subtypes is important in understanding the psychological processes that may be maintaining symptoms (Fond et al., 2014).

The predominant psychological treatment approach for IBS is cognitive behavioural therapy (CBT). The CBT model of IBS suggests that affective factors (e.g. anxiety/worry), unhelpful illness related cognitions and unhelpful behavioural responses perpetuate symptoms and impact quality of life (Hutton, 2005; Kennedy et al., 2005; Spence & Moss-Morris, 2007). An example of an unhelpful illness-related cognition is "*it is embarrassing to keep going to the toilet*". Unhelpful behavioural responses to IBS symptoms may include avoidance behaviours such as avoiding certain foods or social occasions, or safety (also termed 'control') behaviours such as excessive straining on the toilet or carrying extra items when leaving the house in case of symptoms (Reme, Darnley, Kennedy, & Chalder, 2010). More recently a CBT model has been developed in IBS based on the CBT model used in panic disorder (Craske & Barlow, 2006). This aims to target change in gastrointestinal anxiety (also termed 'visceral anxiety') using exposure techniques, cognitive restructuring, attentional control exercises and psychoeducation

[1] CBT, cognitive behavioural therapy; CS-FBD, cognitive scale for functional bowel disorders; BRQ, behavioural responses questionnaire; GI, gastrointestinal; IBS, Irritable bowel syndrome; IBS-A, alternating irritable bowel syndrome; IBS-C, constipation predominant irritable bowel syndrome; IBS-D, diarrhoea predominant irritable bowel syndrome; IBS-U, unclassified irritable bowel syndrome; WSAS, work and social adjustment

about the relationship between the brain and gut (Craske et al., 2011). Such models identify the importance of cognitions and behaviours in maintaining symptoms, but little research has been conducted into the differential role these may have across the IBS subtypes. Each subtype has a particular set of symptoms (Marquis et al., 2014; Fehnel et al., 2017) and these symptoms can have specific psychological effects and effects on outcome (Rønnevig, Vandvik, & Bergbom, 2009). For example the experience of diarrhoea is associated with urgency and unpredictability (Drossman et al., 2009; Rønnevig et al., 2009; Drossman et al., 2011; Håkanson, 2014), which are two unique experiences that may differentiate the psychological responses of those with IBS-D from those with IBS-C.

Understanding whether different subtypes have different affective, cognitive and/or behavioural responses may be important for informing therapeutic assessments and formulations. Increasing understanding in this way can therefore serve to individualise therapeutic strategy to optimise outcomes (Drake, Cimpean, & Torrey, 2009; Hamburg & Collins, 2010; Mönnikes, 2011). Furthermore, there are increasing calls to augment the multidimensionality of diagnostic clinical profiles in IBS (Whitehead, Palsson, & Jones, 2002; Riedl et al., 2008; Polster et al., 2017). As such research investigating whether there are different psychological patterns across bowel subtypes could be used to inform the development of future diagnostic measures.

There have only been four studies to our knowledge that have assessed associations between cognitions and IBS subtypes and three did not find any significant differences between IBS subtypes (Sugaya & Nomura, 2008; Stengel et al., 2010; Thijssen et al., 2010; Windgassen, Moss-Morris, Goldsmith, & Chalder, submitted). The one study that found differences, was also one of only two studies assessing behavioural differences between IBS subtypes (Windgassen et al., submitted). This study assessed IBS-specific behavioural responses and found that those with IBS-D had higher levels of avoidance behaviour than IBS-C, as did those with IBS-A (Windgassen et al., submitted). Those with IBS-A also had higher levels of safety behaviour than IBS-C and IBS-D. The other study assessing behavioural differences across IBS subtypes assessed healthcare- seeking behaviour in IBS subtypes. It found that those with IBS-A had a higher tendency to seek healthcare compared to IBS-C and IBS-D (Katsinelos et al., 2009). There is more research investigating affective factors (anxiety/distress and depression) and personality types (Prior, Maxton, & Whorwell, 1990; Farnam, Somi, Sarami, Farhang, & Yasrebinia, 2007; Eriksson, Andren, Eriksson, & Kurlberg, 2008; Muscatello et al., 2010; Fond et al., 2014; Rey de Castro, Miller, Carruthers, & Whorwell, 2015; Kibune-Nagasako, Garcia-Montes, Silva-Lorena, & Aparecida-Mesquita, 2016). However this has yielded contradictory

findings with regards to which subtype is more or less associated with psychological factors such as anxiety.

The research regarding associations between outcome measures such as symptom severity and quality of life/work and social functioning and IBS subtypes is similarly limited and unclear. However, some studies have suggested that the IBS-A (also referred to as IBS-M for 'mixed IBS') subtype may be a particularly burdensome one (Tillisch et al., 2005; Singh et al., 2015; Kibune-Nagasako et al., 2016). Those with IBS-A have been found to have increased anxiety (Kibune-Nagasako et al., 2016) higher levels of symptom severity and somatisation compared to those with IBS-C and IBS-D (Tillisch et al., 2005). They have also been found to have worse quality of life and impairment of relationships than those with IBS-C (Singh et al., 2015).

A lot of the previous studies assessing psychological differences across IBS subtypes have had small samples, some with as few as 44 participants (Stengel et al., 2010), limiting power to detect significant findings. Furthermore inconsistency in the findings across these studies is likely to be the result of the different criteria used to classify bowel subtypes. Many of the studies were conducted prior to the development of the Rome III criteria coming into use, which substantially altered the parameters for assigning bowel subtype classification when compared to Rome II (Ersryd, Posserud, Abrahamsson, & Simren, 2007). Although the Rome IV criteria are now in use, they remain similar to the Rome III in terms of classification of bowel pattern subtypes (Drossman, 2016).

Hypotheses

The study aimed to assess differences in psychological factors and outcomes across IBS subtypes, in a larger sample with greater power, utilising the clear and validated classification guidelines of the Rome III. We intended to replicate the findings of our previous study, which informed the hypotheses of our present study.

The specific scientific aims were to identify whether levels of unhelpful gastrointestinal (GI) related cognitions or behaviours, general anxiety or depression, work and social functioning and symptom severity differed across IBS bowel pattern subtypes. Based on previous results we hypothesised that (1) unhelpful cognitions would be greater in those with IBS-D than IBS-C (2), unhelpful avoidance behaviours would be greater in those with IBS-D and IBS-A compared to IBS-C (3) safety behaviours would not significantly differ across subtypes. Based on other

previous research we may also expect that individuals with IBS-A have worse outcome measures than the other bowel pattern subtypes.

Method

The present study used baseline and screening data collected as part of the Assessing Cognitive Behavioural Therapy in Irritable Bowel (ACTIB) randomised controlled trial (RCT) assessing the efficacy of CBT in IBS (Everitt et al., 2015). The study compared the efficacy of a high intensity telephone delivered CBT intervention and a lower intensity web-based CBT intervention to a treatment as usual control group. Five hundred and fifty-eight individuals aged 18 and above were recruited from primary and secondary care sites in South London and the South of England. To be included in the trial participants had to meet the Rome III criteria (Drossman, 2006b) for IBS and have a score of >75 on the IBS symptom severity scale (Francis, Morris, & Whorwell, 1997) at screening. Participants also had to have been previously offered first-line therapies, with continuing symptoms of 12 months or longer. Participants were excluded if they had a diagnosis of coeliac disease, inflammatory bowel disease, peptic ulcer disease or colorectal carcinoma. Unexplained rectal bleeding or weight loss also precluded entry from the trial (Everitt et al., 2015). The data for one participant was lost at screening leaving n=557 for analysis in the present paper.

Measures

Classification of IBS Bowel Pattern Subtypes

The Rome III criteria (Drossman, 2006b) was used to assign bowel pattern subtypes (Rome IV is now in use, but had not been developed at the time the ACTIB study commenced). Individuals were classified as IBS-D if they had lose/watery stools ≥ 25% of the time and had hard/lumpy stools < 25% of the time. IBS-C was defined as those with lose stools <25% of the time and hard stools ≥25%. IBS-A was categorised as those with both hard and loose stools ≥25% of the time, while IBS-U experienced hard and loose stools <25%.

IBS Symptom Severity Scale (IBS-SSS)

The IBS-SSS (Francis et al., 1997) is a well validated measure of symptom severity in IBS, measuring the extent of the severity of abdominal and bowel symptoms in terms of frequency and degree of severity. The scale is made up of 5 items with a maximum score of 500. IBS severity is classified as mild for scores between 75 and 175, with scores between 76 and 300

indicating moderate severity. A change in score of ≥50 is considered to be clinically meaningful (Francis et al., 1997).

Work and Social Adjustment Scale (WSAS)

The WSAS (Mundt, Marks, Shear, & Greist, 2002) measures the extent that participation in five areas of life has been affected by the disease in question, with higher scores indicating a higher impact. The five areas of life measured are social activities, private leisure activities, relationships, home and work. Each is measured by one item, scored on a scale of 0 to 8, with a total possible score of 40 across the five items. Scores of 10 and above indicate substantial functional impairment and scores of 20 and above indicate severe impairment (Mundt et al., 2002). The scale has been demonstrated to be a valid and reliable measure of participation in life.

Hospital and Anxiety Scale: Anxiety and Depression (HADS)

The HADs is a measure of general anxiety and depression with a subscale for each construct (Zigmond & Snaith, 1983). Items such as "*I feel tense or wound up*" measure anxiety and items such as "*I feel as if I am slowed down*" measure depression. They are rated on a scale of 0 to 3. Zero indicates strongly disagree and 3 indicates strongly agree. Each subscale consists of 7 items, with a total possible score of 21. Scores of 0-7 are considered normal, whilst scores of 8-10 indicate mild anxiety/depression, 11-14 indicate moderate anxiety/depression, and 15 – 21 severe anxiety/depression. The scale has been demonstrated to have good reliability and validity (Zigmond & Snaith, 1983).

Cognitive Scale for Functional Bowel Disorders (CS-FBD)

The CS-FBD (Toner et al., 1998) is a measure of gastrointestinal specific cognitions consisting of 31 items rated on a Likert scale from 1 to 7, with higher scores indicating a higher degree of unhelpful GI related cognitions. The total score ranges from 31 to 217 with good reliability (α= .93) and validity (Toner et al., 1998). An example of an item assessing GI specific cognitions is "I cannot function normally when I get bowel symptoms".

The Irritable Bowel Syndrome Behavioural Responses Questionnaire (IBS-BRQ)

Behavioural responses to IBS are subdivided into two subscales measuring safety (control) and avoidance behaviours specific to IBS (Reme et al., 2010). An example of an item on the

avoidance behaviour subscale is "*I avoid exercise when I have stomach* pains". An example safety behaviour item is "*I strain when opening my bowels*". The avoidant subscale has 15 items, and the safety subscale has 11 with items rated on a Likert scale of 1 to 7. Higher scores indicate higher levels of unhelpful GI specific behaviours. The scale has been shown to have good reliability and validity α=.86 (Reme et al., 2010).

Analysis

Demographic variables including age, gender, marital status and IBS duration were summarised across the different bowel subtype groups. Differences in continuous demographic variables (age and IBS duration) between IBS subtype groups were assessed using a one-way ANOVA. Differences in categorical demographic variables (gender, marital status and ethnicity) between subtypes were assessed using a Chi Square test of independence.

One-way ANOVAs were used to assess associations between IBS bowel pattern subtypes and each of the psychological variables of interest (dependent variables). To ensure the data met the ANOVA assumptions, normal Q-Q plots were used to assess whether the data was normally distributed and boxplots were used to identify whether there were any outliers for each dependent variable. Homogeneity of variances across subtypes was tested using Levene's test statistic. The F-test statistic was used to assess the overall association between IBS subtypes and the dependent variable using Tukey's Honest Significant Difference (HSD) to evaluate individual comparisons between the subtypes.

Results

The division of the bowel pattern subtypes resulted in just 2.8% of the participant sample (*n*=16) being classified as IBS-U. As this was disproportionately low, IBS-U was excluded from the analysis to preserve sensitivity in finding meaningful differences between groups. Those with IBS-A were the most prevalent 51.4% (*n*=287), followed by those with IBS-D, which constituted 31.9% (*n*=178). Those with IBS-C made up 13.6% of the sample (*n*=76). Table 1 summarises the demographic and illness characteristics across the three subtypes. The only significant difference between groups on these variables was the proportion of females, which were higher in the IBS-C and IBS-A groups (table 1).

Table 1: Demographics across bowel subtype groups

	IBS-C n = 76	IBS-D n = 178	IBS-A n = 287	F/χ^2	P value
Age at randomisation Mean (SD)	45 (12)	43 (13)	42 (12)	1.6	.297
Female gender n (%)	64 (84)	116 (65)	230 (80)		<.001
Ethnicity n (%)				1.6	.454
White	69 (91)	165 (93)	256 (89)		
Other	7 (14)	13 (11)	31 (11)		
Marital Status n (%)				7.3	.119
Single	18 (24)	37 (21)	90 (31)		
Married/Cohabiting	51 (67)	122 (69)	176 (61)		
Widowed/separated/divorced	7 (9)	19 (11)	21 (7)		
IBS duration mean n (SD) in years	10 (8)	10 (9)	11 (10)	0.2	.801

SD = standard deviation, χ^2 *in italics*

Assumption violations and outliers in dependent variables of interest

Some of the dependent variables were not normally distributed in the different IBS subtype groups. CS-FBD was mildly negatively skewed in the IBS-A group, while r the safety subscale of the BRQ had negative kurtosis in the IBS-C group. WSAS had negative kurtosis in all bowel subtype groups. None of the data was severely skewed. As one-way ANOVAs are quite robust to mild deviations from normality, particularly in large sample sizes, no transformations were made to the data. A number of outliers were identified for all dependent variables apart from symptom severity. These were checked to ensure they were not the result of data entry and measurement error. The most extreme outliers were removed and the analysis was rerun to

determine if inclusion of the outliers had substantially changed the results. They did not, so the outliers were included in the final analysis.

Cognitive and behavioural differences between IBS-C and IBS-D

A significant difference between subtypes was found for GI related cognitions F(2, 538), 3.50, p = .031. Tukey's HSD post hoc comparisons identified that IBS-C and IBS-D significantly differed (MD = 11.8, p=.026, 95% CI 1.1, 22.5) with IBS-D having significantly higher levels of unhelpful GI related cognitions (figure 1). Figure 1 demonstrates that there was also a difference between IBS-C and IBS-A, which approached statistical significance, while there was no difference in GI cognitions between IBS-A and IBS-D subtypes.

A significant difference between subtypes was also found for GI related avoidance behaviours F(2, 538), 10.25, p<.001, with IBS-D showing significantly higher levels of avoidance behaviours than IBS-C (MD = 11.0, p<.001, 95% CI 5.3, 16.7). Those with IBS-A also had significantly higher levels of avoidance behaviours than IBS-C (MD = 7.7, p=.002, 95% CI 2.3, 13.1). Figure 2 illustrates that the group contrasts.

Safety behaviours also significantly differed across groups F(2, 538), 10.55, p<.001. Post hoc tests indicated that IBS-C showed significantly higher levels of safety behaviours than those with IBS-D (MD = 4.6, p=.004, 95% CI 1.3, 8.0) as did those with IBS-A (MD =4.3, p<.001, 95% CI 2.0, 6.6) (figure 3).

Comparable factors across IBS subtypes

There were no significant differences between IBS subtypes for anxiety, work and social adjustment or IBS symptom severity (table 2).

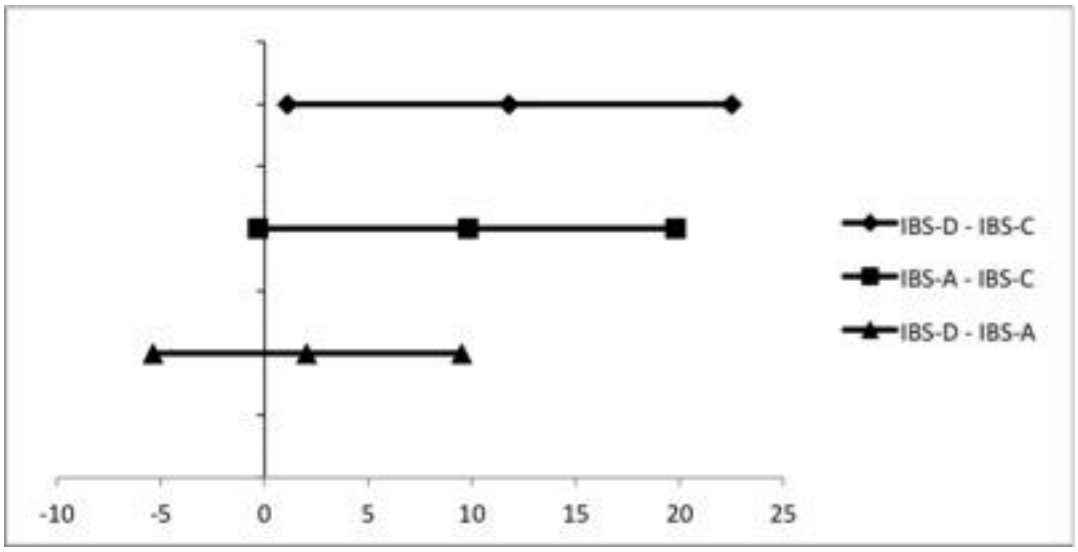

Figure 1: Mean differences in GI related cognitions with upper and lower 95% confidence limits across groups

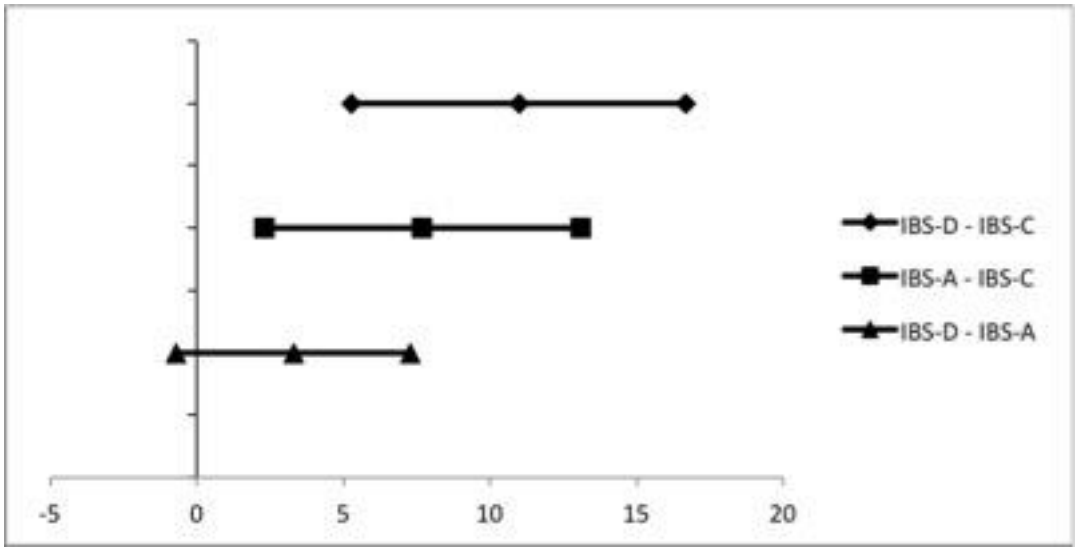

Figure 2: Mean differences in GI related avoidance behaviour with upper and lower 95% confidence limits across groups

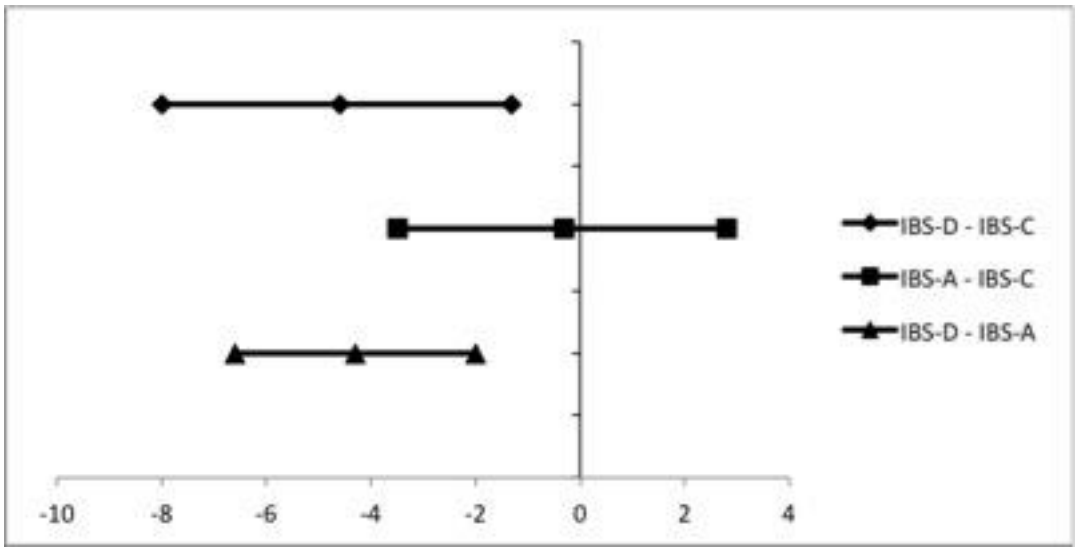

Figure 3: Mean differences in GI related safety behaviour with upper and lower 95% confidence limits across groups

Discussion

IBS bowel pattern subtypes were generally comparable across demographic variables, with the exception of gender. There was a significantly higher proportion of females with IBS-A and IBS-C than those with IBS-D. Although IBS subtypes did not differ in terms of symptom severity, work and social adjustment and levels of anxiety and depression, there were cognitive and behavioural distinctions between groups. Those with IBS-A and IBS-D experienced a greater degree of unhelpful GI-related cognitions than those with IBS-C. Results also indicated a contrast in the type of behavioural responses that patients with IBS-C and IBS-D engage in. While those with IBS-D engage in more avoidant behaviour in response to symptoms, those with IBS-C instead utilise more safety behaviours. IBS-A was shown to have significantly higher levels of avoidance behaviours compared to IBS-C and safety behaviours compared to IBS-D.

Table 2: Mean differences in psychological outcomes between IBS subtypes

	F	P_1	Group Contrast	Mean Difference	P_2	95% CIs Lower Limit	Upper Limit
Symptom Severity	1.7	.19	IBS-C – IBS-D	-6.1	.26	-15.2	3.0
			IBS-C – IBS-A	-1.9	.86	-10.5	6.6
			IBS-A – IBS-D	-4.2	.27	-2.2	10.5
Work and Social Functioning	0.6	.58	IBS-C – IBS-D	-0.8	.79	-3.5	2.0
			IBS-C – IBS-A	0.1	>.99	-2.5	2.7
			IBS-A – IBS-D	-0.8	.56	-1.1	2.7
Cognitions	3.5	.031	IBS-C – IBS-D	-11.8	.026	-22.5	-1.1
			IBS-C – IBS-A	-9.8	.060	-19.8	0.3
			IBS-A – IBS-D	-2.0	.80	-5.4	9.5
Avoidance Behaviours	10.3	<.001	IBS-C – IBS-D	-11.0	<.001	-16.7	-5.3
			IBS-C – IBS-A	-7.7	.002	-13.1	-2.3
			IBS-A – IBS-D	-3.3	.13	-0.7	-7.3
Safety Behaviours	10.4[a]	<.001	IBS-C – IBS-D	4.6	.004	1.3	8.0
			IBS-C – IBS-A	0.3	.97	-2.8	3.5
			IBS-A – IBS-D	4.3	<.001	2.0	6.6
Anxiety	.8	.43	IBS-C – IBS-D	0.7	.41	-0.6	2.1
			IBS-C – IBS-A	0.6	.50	-0.7	1.9
			IBS-A – IBS-D	0.1	.95	-0.8	1.1
Depression	1.3	.27	IBS-C – IBS-D	0.7	.33	-0.5	1.9
			IBS-C – IBS-A	0.7	.26	-0.4	1.9
			IBS-A – IBS-D	-0.03	>.99	-0.9	0.8

F, F statistic; [a], Welch statistic; P_1, significance of one way ANOVA between groups at 0.05 level; P_2, significance of one way ANOVA post hoc comparisons at standard significance level 0.05; CIs, confidence intervals

Similarities and distinctions between IBS-A and IBS-D

The finding that individuals with both IBS-A and IBS-D have higher avoidance tendencies than IBS-C, may be understood in terms of the similarities in symptom profiles. Both experience diarrhoea, which is a particularly disruptive symptom that is often accompanied by a sense of urgency or lack of control. These individuals may choose to avoid situations or stimuli that decrease the likelihood of control. The CBT model of IBS highlights the bidirectional relationship between avoidance and unhelpful GI related cognitions (Hutton, 2005). Unhelpful thoughts about the potential impact of symptoms such as 'it is embarrassing to keep going to the bathroom' are likely to increase avoidant tendencies. Simultaneously, avoidance increases the propensity to engage in unhelpful thinking patterns about bowel symptoms as individuals are deprived

of experiences that could counter unhelpful negative thinking regarding symptoms (Olatunji, Etzel, Tomarken, Ciesielski, & Deacon, 2011).

Previous studies have demonstrated the association between unhelpful cognitions and behaviours in IBS (Rutter & Rutter, 2002; Reme et al., 2010; Reme et al., 2011). Our previous study also suggested that unhelpful cognitions and behaviours were generally associated (Windgassen et al., submitted). Our finding that IBS-D had significantly higher levels of both avoidance behaviours and unhelpful cognitions is consistent with this. Whilst those with IBS-A had significantly higher levels of avoidance behaviour than participants with IBS-C, their levels of unhelpful cognitions were not significantly higher. The elevated level of unhelpful GI cognitions associated with IBS-D may be rooted in the differential experience of symptoms compared to the other two subgroups (Casiday, Hungin, Cornford, de Wit, & Blell, 2008; Rønnevig et al., 2009). Some studies have suggested that those with IBS-D have more visceral sensitivity (Prior et al., 1990; Elsenbruch & Orr, 2001; Kanazawa et al., 2008), which may at least partially contribute to elevated levels of unhelpful cognitions.

The finding may however be due to measurement bias. This may have arisen as some items of the CS-FBD relate more specifically to individuals with IBS-D than those with IBS-C. For example, items such as "*I often worry that there may not be a bathroom when I need one*" would not be relevant to individuals experiencing constipation. The possibility of measurement bias nevertheless highlights the importance of developing measures that account for the experience of each bowel subtype in IBS. This is increasingly recognised amongst researchers and collaborative working groups in IBS with regards to outcome measures (Fehnel et al., 2017). Our paper may suggest that this is important also for psychological and process measures developed for IBS.

Behavioural differences

The behavioural differences between IBS-D and IBS-C are reflective of the type of bowel symptoms experienced in each. It makes intuitive sense that those with IBS-D may be more avoidant in case of a toileting accident. However, those with IBS-C may seek to exert more control over their bowel by facilitating bowel movements using various safety behaviours (e.g. straining, stool checking, eating certain types of food to stimulate the bowels). These results partially replicate our previous findings (Windgassen et al, submitted) in that those with IBS-D were significantly more avoidant than IBS-C. However, novel to the present study was the finding that participants with IBS-C had significantly more safety behaviours than those with IBS-D.

Due to the stark contrast in behavioural associations between IBS-D and IBS-C we investigated whether the findings were due to measurement bias, supposing that the number of safety and avoidance subscale items could have been weighted towards the respective bowel pattern subtypes. For instance the item 'I often go to the toilet and do not pass anything' (item 7 of the BRQ) may only be applicable to those with constipation. However, inspection of the subscale items shows that there are an equivalent number of safety items relating to both types of symptom.

A notable finding was that those with IBS-A appeared to have 'the worst of both worlds' in terms of having significantly higher levels of avoidance behaviour than those with IBS-C (along with IBS-D) and significantly higher levels of safety behaviour than those with IBS-D (along with IBS-C). Given the behavioural distinctions between IBS-D and IBS-C, it makes sense that individuals with alternating diarrhoea and constipation use both types of behaviour in an effort to cope with both types of symptoms.

Differences in psychological but not outcome factors

IBS-A has previously been characterised as being particularly burdensome (Tillisch et al., 2005; Singh et al., 2015; Kibune-Nagasako et al., 2016). Although our results partially support this in terms of this subtype having increased types of both maladaptive behaviours, they did not have worse outcomes with regards to symptom severity, work and social adjustment or anxiety and depression. Indeed, none of the IBS subtypes were found to differ in terms of these outcomes.

This is in line with other previous findings (Simren, Abrahamsson, Svedlund, & Björnsson, 2001; Mönnikes, 2011; Jamali et al., 2012; Rey de Castro et al., 2015). As such we may conclude that in general subtypes are not associated with different levels of symptom severity, or psychological comorbidity. A previous study assessing subgroups in IBS using cluster analysis, instead found that whilst there are distinct bowel pattern subtypes in line with Rome III and IV criteria, these were further divided into those with high or low psychological and somatic comorbidity subgroups (e.g. IBS-A high comorbidity, IBS-A low comorbidity, etc.) (Polster et al., 2017). Therefore, it may be of more value to investigate the difference in outcomes between subgroups more comprehensively defined by a number of factors including psychological comorbidity. The authors of this study found that subgroups with higher rated comorbidities were associated with higher levels of symptom severity also (Polster et al., 2017).

Clinical implications

In terms of informing psychological treatment approaches, the results suggest that individuals experiencing IBS-D may benefit from techniques focussing on addressing unhelpful cognitions, at least as identified in the CS-FBD. Those with IBS-D and IBS-A would appear to benefit from behavioural strategies targeting avoidance behaviours. In addition, techniques targeting a reduction in safety behaviours may be particularly transformative for individuals with IBS-C and IBS-A. Safety behaviours as measured by the BRQ include tendencies to eat specific foods to help open the bowels, checking for blood in stools and spending more time on the toilet than individuals would ideally like. The importance of changing cognitions and behaviours in IBS has previously been indicated in mediation studies (Windgassen et al., 2017). Future studies may seek to assess whether outcomes of psychological treatment for IBS may be differentially affected in this subtype using moderation analysis.

Given the potential of measurement bias, the results also highlight the importance of considering the validation of psychological measures developed for IBS in application to the different IBS subtypes. Recent developments of IBS subtype specific outcome measures demonstrate the importance and utility of tailoring such measures (Fehnel et al., 2017).

Finally, the present study supports the need for more comprehensively classified subgroups in the IBS field based on additional characteristics such as psychological factors (Whitehead et al., 2002; Polster et al., 2017). Increasing the dimensionality of subgroups can provide further understanding of heterogeneity in IBS.

Limitations

There were several limitations of our study relating to the statistical tests used. Ideally for one-way ANOVAs to adequately identify statistical differences between groups, the dependent variable should be normally distributed and yet for some of the outcome measures in our study, they were not. However, a non-parametric alternative to ANOVA, the Kruskal-wallis test, was also run which verified the results of the ANOVA.

A difficulty with investigating the role of bowel pattern subtypes in IBS is that bowel subtypes have been demonstrated to fluctuate and change (Palsson, Baggish, Turner, & Whitehead, 2012). As such it is not clear whether the associations found in the present paper would also change in accordance to any fluctuations with bowel pattern changes

within subjects. Another difficulty in the assessment of bowel pattern subtypes is that different versions of the Rome criteria differentially classify the subtypes (Drossman, 2006a). The present study used the Rome III criteria to categorise subtypes. However, the latest guidelines for classification is the Rome IV (Drossman, 2016). Rome IV states that subtypes are to be based on symptomatic stools only. This is likely to substantially shift the prevalence of each type of subtype.

The sample of participants used in the present study has refractory IBS and were prepared to enter a CBT trial. This sample therefore may not be representative of the population of individuals with IBS

Conclusion

The present paper replicated our previous paper (Windgassen et al., submitted) demonstrating that although subtypes did not differ in terms of levels of symptom severity or distress, there were distinct cognitive and behavioural responses between groups. The results may be important for informing assessment and formulation in psychological therapies for IBS. Cognitive and behavioural responses may also be important for inclusion in more multidimensional characterisation of diagnostic subgroups in IBS.

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Baseline measure of the total sample in data set 2

Variables	**Mean**	**Standard Deviation**
Symptom severity	265.0	95.5
Work and social adjustment	12.5	8.5
GI related cognitions	150.2	33.5
GI related avoidance behaviours	51.3	18.1
GI related safety behaviours	46.4	10.6
Anxiety	10.7	4.2
Depression	5.7	3.7

8.3 Summary

This study replicated the analysis of study three with a few key differences aimed to improve the quality and validity of the analysis. These differences included the use of a greater sample size of participants meeting the more recent Rome III criteria rather than Rome I criteria. This allowed the classification of bowel subtypes to follow the official stipulation of the Rome III and IV diagnostic criteria (Drossman, 2006; Drossmanm 2016). Both study three and four found that those with IBS-D and IBS-A had significantly higher levels of avoidance behaviour than those with IBS-C. There was however a distinction in the findings of study three and four regarding safety behaviours. In study three it was found that only those with IBS-A had higher levels of safety behaviours than the other two subtypes, whereas in study four both IBS-A and IBS-C had higher levels of safety behaviour than IBS-D. Another more consistent distinction between findings of study three and four was that the non-significant trend for a greater level of unhelpful GI related cognitions in IBS-D than IBS-C found in study three, became significant in study four.

Study four therefore supports the conclusion of study three that there are distinct cognitive and behavioural patterns across the different IBS subtypes. The potential of measurement bias accounting, at least in part, for some of these results was raised as a possibility. Validation of measures across the different IBS subtypes is suggested to assess this further. In line with a more recent study, the results suggest that bowel pattern subtypes are important in distinguishing subgroups in IBS but psychological factors are also important in the characterisation of these subgroups (Polster et al., 2017). To further these findings, cluster analysis such as latent class analysis could be used to assess the existence of subgroups in IBS as characterised by bowel pattern subtypes, cognitive, behavioural and affective factors.

9. Discussion

9.1 Chapter Overview

The studies conducted in this thesis were designed to assess the importance of cognitive and behavioural factors in irritable bowel syndrome (IBS). Two of the studies examined the potential mediating roles of cognitive and behavioural factors in CBT for IBS (chapters four and five). Chapter four systematically reviewed the literature on factors that mediated the treatment effect in trials evaluating psychological interventions for IBS. Chapter five assessed simple and sequential mediation models including process variables informed by the cognitive behavioural models of IBS. The results of these studies indicated that gastrointestinal (GI) cognitions appeared to be particularly important mediators of treatment effect on the outcomes of symptom severity and quality of life (QoL)/ work and social adjustment (WSA). There was some evidence for the mediating roles of gastrointestinal specific anxiety (GSA), general anxiety and GI related behaviours.

The two subsequent studies, three and four, investigated whether cognitive and behavioural factors in addition to other psychological and outcome measures, were differentially associated with bowel pattern subtypes in IBS (chapters seven and eight). Results utilising data from two separately conducted RCTs were largely similar. The different subtypes were associated with different cognitive and behavioural tendencies. A key difference was that in the larger RCT (Everitt et al., 2015), individuals with IBS-C had higher levels of safety behaviours than those with IBS-D. Neither of the studies found significant differences in physical and affective outcomes.

The theoretical and clinical implications of all these results are discussed further. The results of the studies assessing mechanisms of treatment effect are considered in section 9.2, and the results of studies assessing associations between subtypes and cognitive and behavioural factors are considered in section 9.3. A general discussion of the strengths and limitations of the studies and the implication for future research and clinical directions is also provided in section 9.4.

9.2 Assessing Mechanisms In IBS

9.2.1 Revisiting the aims of study one and two

The objective of study one and two was to assess whether cognitive and behavioural factors were mediators of treatment effect on the outcomes of symptom severity and work and social adjustment/QoL.

9.2.1.1 Systematic review (study one) aims

The aim of study one was to systematically identify psychological factors found to mediate the effect of psychological interventions for IBS on the outcomes of symptom severity and/or QoL. It was hypothesised that cognitions, behaviours and anxiety would be found to significantly mediate treatment effect, in line with cognitive behavioural (CB) models of IBS (Kennedy et al., 2005; Craske & Barlow, 2006; Moss-Morris, McAlpine, Didsbury, & Spence, 2010).

9.2.1.2 Mediation analysis (study two) aims

Study two had two specific aims: (1) to assess whether GI related avoidant and safety behaviours, GI related cognitions and general anxiety, mediated the effect of CBT on symptom severity and WSA; (2) to identify which mediating variables changed first in sequential mediator models. It was hypothesised that all four variables would significantly mediate the effect of CBT on both outcomes based on the CB models of IBS and findings from previous studies (Windgassen et al., 2017). It was also hypothesised that cognitive and behavioural change would precede change in anxiety, as these were the targets for change in the treatment protocol informed specifically by the three systems model (1.13.1). Furthermore in the previous mediation study based on the same data, cognitive and behavioural change was found to precede changes in anxiety (Reme et al., 2011).

9.2.2 Summary of systematic review (study one)

In four out of five studies, cognitions were found to mediate the treatment effect in terms of symptom severity. Five studies also assessed GSA as a mediator, with three finding significant mediation and one finding a trend towards significance. Only one of three studies that assessed general anxiety as a mediator found significant mediation. This was a more complex analysis where the effect of moderators were assessed simultaneously. Anxiety was only found to significantly mediate treatment in participants with low

baseline quality of life (QoL) (Labus et al., 2013). Of the two studies assessing behavioural responses, the one that significantly mediated change, assessed IBS specific behavioural coping responses. There was a similar trend in results for the mediation analysis with QoL as an outcome.

9.2.3 Summary of mediation analysis (study two)

Chapter five described the mediation analysis conducted using data from a previously reported RCT (Kennedy et al., 2005). The RCT compared CBT + mebeverine compared to mebeverine alone in GP diagnosed IBS patients meeting the Rome I criteria. The simple mediation models found that general anxiety, GI related cognitions and safety behaviours significantly mediated the treatment effect on the outcomes of symptom severity and WSA. Avoidance behaviour was not a significant mediator. Sequential models found that GI related cognitions and safety behaviours changed prior to a reduction in anxiety and that this meditational path accounted for improvement in symptom severity and WSA. These sequences were found to fit best for both outcomes according to the prioritised assessment of fit criteria.

9.2.4 How results inform theory

Theoretical models are devised to explain potential relationships between explanatory variables and outcomes such as symptoms, mood and/or disability. While the use of CBT has been found to be effective in improving such outcomes in IBS (Ford et al., 2009; Ford et al., 2014), the mechanisms of efficacy are not as commonly assessed (Windgassen et al., 2016; Windgassen et al., 2017). As presented in chapter one (section 1.13) there are a number of different CB models that have been adapted for IBS. All of the models assert that cognitions and behaviours interact to maintain symptom severity and impaired functioning/QoL. The four-factor model (1.13.2) and the CBT-IE model (1.13.3) respectively identify general anxiety and gastrointestinal specific anxiety (GSA) as also interacting with cognitions and behaviours to maintain symptoms. The three system's model (Lang, 1968) (1.13.1) in contrast, omits the role of anxiety as a key mediating factor. Instead it identifies GI related cognitions, behaviours and physiological responses as the processes that interact to maintain symptoms. The CBT provided in study two followed the three system's approach (Kennedy et al, 2005) and this was the model primarily assessed in the present thesis.

Although the studies in this thesis focussed on the three system's model of IBS and more generally the CB models of IBS, there are a number of alternative health

psychology models that could be applied to understand the perpetuation of IBS symptoms and disability. The model that perhaps has the most parallels with the CB models of IBS is the 'Common Sense Model' (CSM) (Leventhal, Brissette, & Leventhal, 2003). This model posits that individuals utilise different sources of information that may be concrete (such as information provided by doctors) or abstract (such as internal beliefs) to inform mental (or cognitive) representations of their illness. There are six dimensions of illness representations: identity, cause, timeline, consequence, control and coherence. 'Identity' is the label given to illness, such as the medical diagnosis and symptoms patients believe to be associated with that label. 'Cause' refers to the perceived cause of the illness, whether it is biological such as a bacterial infection or psychological, such as stress. Individuals may also believe there are multiple causes including biological, psychological and social factors. 'Timeline' representations are beliefs about the likely duration of an illness and whether it is acute, chronic and/or cyclical. 'Consequences' describes the individuals' judgements on the impact that the illness will have on their life. 'Control' has been subdivided into 'treatment control' and 'personal control' (Broadbent, Petrie, Main, & Weinman, 2006). Treatment control is the degree of control individuals believe that they have over their treatment, which may pertain to the degree of side effects they perceive to be associated with the treatment, the number of treatment options and the perceived efficacy. Personal control in contrast is the degree of control that the individual personally believes they can exercise over their illness. Finally, 'coherence' refers to the extent to which individuals understand their illness.

In addition to cognitive representations, the model posits that the experience of illness also causes emotional representations such as fear, worry or sadness, and that together cognitive and emotional illness representations influence coping behaviours. The model advocates parallel processes whereby cognitive and emotional representations influence coping strategies via two different pathways (figure 9.1). Coping behaviour can be helpful or unhelpful, including but not limited to strategies such as avoidance or denial, expressing emotion, problem-focused coping and seeking social support (Hagger & Orbell, 2003). The final stage of the model is the appraisal of coping strategies as either effective or ineffective. These appraisals feed back to individuals' illness experience and further representations of their illness. Appraisals therefore have the potential to change the use of coping strategies. The CSM has been used to explain a range of outcomes in long-term conditions including disease state, physical functioning and psychological distress (Hagger & Orbell, 2003), including IBS (Rutter & Rutter, 2002, 2007).

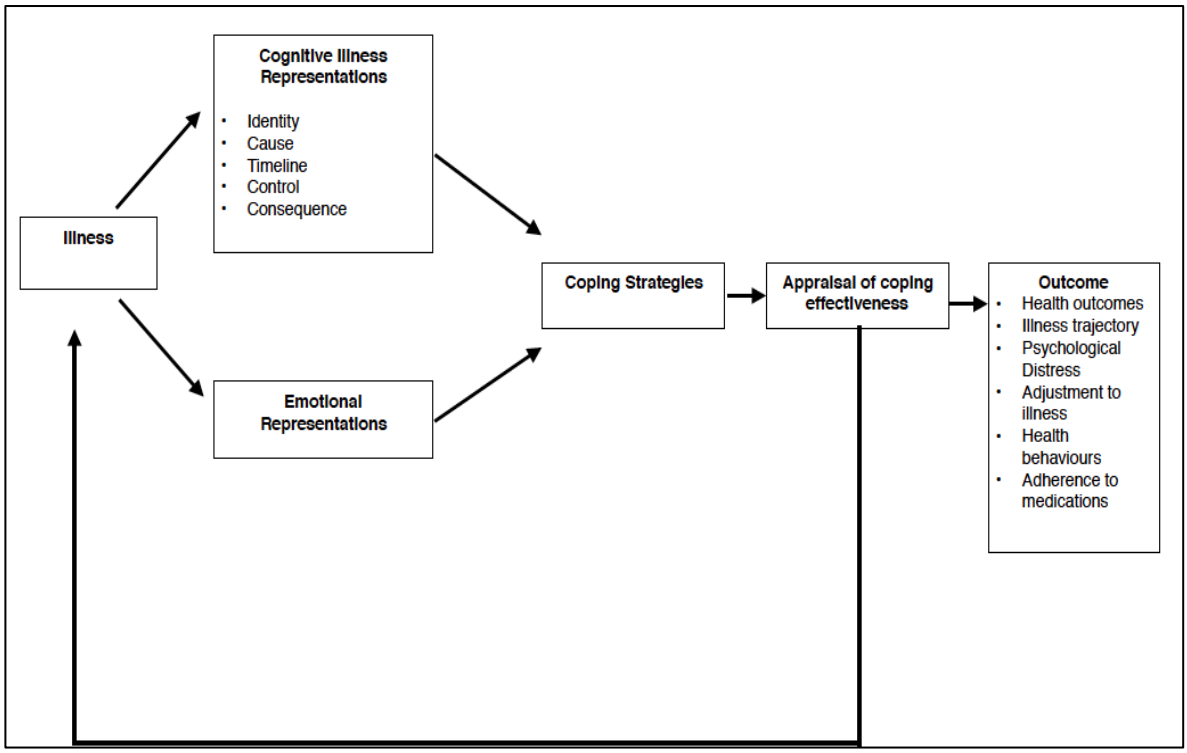

Figure 9.1: Common Sense Model of Illness adapted from 'Improving uptake of cardiac rehabilitation: Using theoretical modelling to design an intervention' by S.M Molesh, 2009, *European Journal of Cardiovascular Nursing, 8 (2009),* 161-168, pg 164.

Both the CSM and the CB models of IBS identify similar process variables that impact on outcomes. The CB models of IBS identify GI related cognitions and GI related behavioural responses as key factors contributing to outcomes. Similarly, the CSM identifies illness representations, appraisals of coping strategies (i.e. cognitions) and coping strategies (i.e. behaviours) as key processes. The four-factor and CBT-IE models of IBS also share with the CSM the identification of affective factors as important processes impacting on outcomes.

It may be argued that processes identified in the CSM are more general, while the processes in the CB models are more specific to the experience of IBS. For example an illness representation may pertain to general perceptions of the degree of control an individual has over their IBS symptoms. An example coping behaviour may be broadly described as tendencies to engage in emotion-focussed coping. In contrast unhelpful GI related thoughts and behaviours considered in the CB models of IBS have more specificity to the day-to-day experience of IBS. These include thoughts and behaviours such as '*I am constantly frustrated by my bowel symptoms*' and '*I avoid exercise when I have stomach pains*'.

The two models also contrast in the posited relationships between variables. While the CB models postulate that emotions, cognitions and behaviours interact with each other in a non-linear fashion, the CSM asserts a directional relationship between the factors. Namely, the CSM asserts that cognitions inform behaviours, which subsequently impact on appraisals of coping and illness outcomes (Rutter & Rutter, 2002). Furthermore in the CSM, emotional representations are purported to occur in parallel to cognitive illness representations, with no relationship identified between cognitions and emotions. Behaviours are therefore said to be affected by emotions and cognitions independently (figure 9.1). The partitioning of cognitions and emotions in this way is not intuitive, as experientially we can witness the interplay between emotions and cognitions on a daily basis. For instance, if an individual has the thought *'I do not have the resources to cope with this*', it is likely to cause anxiety or feelings of worry or dread. Similarly, if individuals experience low mood this may have an impact on an individual's cognitive perception of their ability to cope with a particular event. Indeed the interplay between cognitions and emotions in this way has been well demonstrated (Kark Smollan, 2006; Deary, Chalder, & Sharpe, 2007; Chida, Hamer, & Steptoe, 2008). Furthermore, proposed updates to the models by the authors include the integration of emotional and illness representations at the different 'stages' (representation, coping, appraisal) (Leventhal, Diefenbach, & Leventhal, 1992).

Both the systematic review and mediation analysis identified the mediating role of illness related cognitions in IBS. Therefore the results provide some support for all of the adaptations of the CB models of IBS as well as the CSM. Although the constructs assessed in the IPQ-R adapted for IBS (Chilcot & Moss-Morris, 2013; Everitt et al., 2015) are more generic than those assessed in the CS-FBD (Toner et al., 1998) there appears to be overlap between the constructs. For instance the item from the CS-FBD *'I cannot function normally when I get bowel symptoms'* is likely to overlap with the symptom control item in the CSM i.e. *'How much control do you feel you have over your IBS symptoms?*' Similarly, the item related to timeline in the IPQ-R '*I often feel that this abdominal pain will never go away*' is reasonably specific. Broadly speaking, the results endorse the idea that changing the way individuals think about their illness has an effect on the outcomes of that illness. Thus both CB models and CSM have some validity.

The systematic review was not able to assess the extent to which behaviours were important for causing change in outcome as only two of nine studies assessed the mediating role of behaviours. One study (Chilcot & Moss-Morris, 2013) used a measure

of ‘all-or-nothing’ behaviour (Skerrett & Moss-Morris, 2006), which includes items such as ‘*I tend to overdo things and then rest up for a while’*. This was not found to mediate treatment effect on symptom severity. In contrast the other study included in the review assessed GI related behavioural responses (Reme et al., 2011). This study found that safety and avoidance behaviours combined into a total score were significant mediators of treatment effect. However, in the more nuanced mediation study (see chapter five) GI safety behaviours rather than avoidance behaviours were found to mediate the treatment effect (discussed in 9.2.5). The results of both study one and two therefore partially support the CB models of IBS and the CSM as behaviours were shown to influence outcomes. However, the results lend more support to the CB models of IBS than the CSM, in that they indicate the importance of specifically GI related behaviours rather than more general unhelpful cognitions or coping behaviours.

The assertion of the CSM, four-factor and CBT-IE models of IBS, that affective factors also influence outcomes was supported by both mediation studies. The systematic review identified GSA as a potentially important mediator. The mediation study carried out as part of this thesis identified general anxiety as a significant mediator of the treatment effect. Both studies lend support to the hypothesis in the biopsychosocial model of IBS that anxiety is one of the underlying process by which psychological factors have physiological effects (Mach, 2004; Fichna & Storr, 2012; Stasi, Rosselli, Bellini, Laffi, & Milani, 2012). However the results also show that changing GI cognitions and behaviours brings about change in anxiety (discussed further 9.2.5.2). Therefore the three system’s model may have the benefit of identifying which factors are important to target for change (cognitions and behaviours). Meanwhile the four-factor model and CBT-IE model have the benefit of making the distinction between anxiety and symptoms, which can increase clarity regarding how treatments work to change symptoms.

9.2.5 How results inform clinical practice

There are three main clinical implications from the findings of study one and two (1) the importance of targeting change in psychological factors specific to the experience of IBS; (2) the prioritisation of changing GI related cognitions and safety behaviours over the targeting of general anxiety and (3) the apparent importance of tackling safety behaviours. Each of these clinical implications are considered further below. An updated three system’s formulation is depicted in figure 9.2 based on the results.

9.2.5.1 The importance of targeting change in psychological factors specific to the experience of IBS

Both studies specifically highlighted the importance of changing illness-related cognitions as opposed to general unhelpful cognitions. In study one most measures of cognitions were illness/GI specific such as the use of the cognitive scale for functional bowel disorders (CS-FBD) (Reme, Darnley, Kennedy, & Chalder, 2010). Study two also used the CS-FBD, which assessed unhelpful cognitions specifically related to GI symptoms such as abdominal pain and bowel movements. It included items such as '*I often worry that there may not be a bathroom when I need it*' or *'I am constantly frustrated by my bowel symptoms*'. The combined results therefore indicate the importance of changing negative thoughts specifically relating to the experience of IBS in order to improve outcomes. Similarly both studies suggest that changing behaviours specific to IBS are important for changing outcomes. Study one found that GI specific behaviours mediated treatment effect whereas non-IBS specific 'all-or-nothing' behaviours did not (Chilcot & Moss-Morris, 2013). Study two indicated that specifically GI related safety behaviours mediated treatment effect on outcomes. Finally, GI *specific* anxiety was shown to mediate treatment effect more often than general anxiety in the systematic review. Together these results highlight the importance of assessing psychological factors specifically relating to the experience of IBS.

9.2.5.2 The prioritisation of changing GI related cognitions and safety behaviours over general anxiety

The results of the sequential models suggest that GI related cognitions and GI safety behaviours changed in order to reduce general anxiety. This makes intuitive sense as a reduction in negative GI related thoughts such as '*I cannot cope with these bowel symptoms*' is likely to alleviate anxiety that would have been associated with these thoughts. The impact of negative cognitions on predicting anxiety is established across healthy and illness populations (Brosschot, Gerin, & Thayer, 2006; Eysenck, 2014). Furthermore, the need to reduce safety behaviours in order to facilitate a reduction in anxiety is well documented in the literature on anxiety disorders and health anxiety (Beesdo‐Baum et al., 2012; Helbig-Lang et al., 2014; Goetz, Davine, Siwiec, & Lee, 2016).

These findings are important to consider when developing detailed treatment manuals specifically for improving symptoms and disability related to IBS. Models for understanding and treating IBS are different to those currently being used for anxiety

disorders. Clinicians in services such as Increasing Access to Psychological Therapies (IAPT) may be tasked with targeting general anxiety in individuals with IBS, assuming that reduction of general anxiety will cause IBS symptoms to subside. However, the results of the thesis suggest that targeting IBS specific cognitions and behaviours is important.

9.2.5.3 The apparent lack of emphasise on changing avoidance behaviours

The finding that avoidance behaviour did not significantly mediate treatment effect was a surprising one. Avoidance behaviour items included '*I avoid going out in case I have problems with my IB*S' and '*I avoid certain work situations (e.g. meetings) because of my IBS'*. While these behaviours did change during CBT, there was greater change in safety behaviours (chapter 5, table 2). One potential explanation for this finding is that participants were not particularly avoidant at baseline reducing the scope for change. This is supported by the fact that at baseline avoidance behaviours were moderate in the Kennedy trial (Kennedy et al., 2005), with a mean score (SD) of 44.5 (17.3) out of a potential total score of 105. The baseline avoidance (M=51, SD=18.1) was not much higher in the ACTIB study (data set 2), which recruited individuals with refractory IBS (IBS resistant to treatment and of long duration). As such avoiding daily activities may not be something that this patient population engage in particularly. Indeed, there appears to be a trend for the opposite in IBS, with individuals adopting a stoic 'just get on with it' attitude, taking great efforts not to allow the condition to take over their lives (Casiday, Hungin, Cornford, de Wit, & Blell, 2008; Håkanson, 2014). However, baseline levels of safety behaviours were also moderate (M=44.7, SD=10.7) and these were still found to be significant mediators. Furthermore, the direct effect of CBT on avoidance and safety behaviours was significant, indicating that therapy reduced both variables (chapter 5, table 2). The distinction was that the change in safety behaviours did result in change in outcomes, whereas change in avoidance behaviours did not.

The fact that avoidance did not mediate the treatment effect does not preclude it from having a mediating effect in conjunction with other mediating variables. For example CBT may reduce avoidance behaviour, which in turn reduces anxiety and this sequence causes change in outcome. In this analysis, avoidance behaviour was not included in sequential mediation models for two reasons: (1) the non-significance in simple mediation models and second; (2) to avoid data dredging (Breitborde, Srihari, Pollard, Addington, & Woods, 2010). Nevertheless it remains a possibility that avoidance behaviour could mediate treatment effects in future studies. In the meantime the results

indicate that clinicians may be wise to prioritise change in safety behaviours over change in avoidant behaviours.

Should future studies replicate the finding that the reduction of avoidance is not a key factor in reducing symptom severity or increasing work and social functioning in IBS, this would have implications for treatment model development (Kazdin, 2009; Holmes et al., 2018). The current three systems CBT approach for IBS may be modified by specifying that key unhelpful illness related *control* behaviours play a role in the maintenance of IBS symptoms rather than avoidance behaviours. This would have an impact on the use of treatment techniques, many of which are designed to reduce avoidance and the anxiety that is perpetuated by such avoidance. Instead therapeutic focus may be on the response prevention and cognitive restructuring as used in OCD (Olatunji, Davis, Powers, & Smits, 2013). Alternative potential mechanisms are considered in more detail in section 9.4.6.

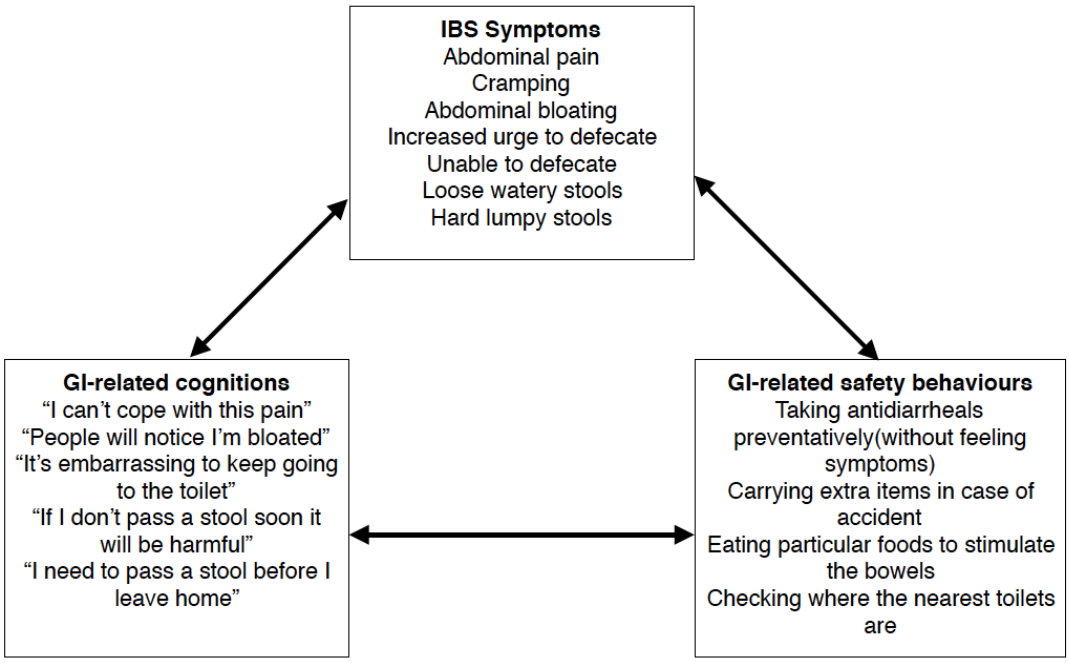

Figure 9.2: Adapted three systems formulation model based on study two results

9.3 Assessing Psychological Differences in IBS Subgroups

9.3.1 Revisiting the aims of study three and four

The overall objective of studies three and four was to identify cognitive and behavioural factors associated with IBS bowel pattern subtypes. Both studies aimed to assess whether there were differences in cognitive and behavioural factors in addition to levels of anxiety, depression, symptom severity and WSA, across IBS subtypes.

9.3.1.1 Assessing psychological and outcome differences in subtypes (study three) aims

It was hypothesised that due to the nature of symptoms and the additional burden created by the experience of diarrhoea, those with IBS-A and IBS-D would have more extreme symptoms, disability and cognitive, behavioural responses compared to those with IBS-C. It was also hypothesised that IBS-A would have higher levels of abdominal pain than the other subtypes due to previous findings (Heitkemper et al., 2011).

9.3.1.2 Assessing psychological and outcome differences in subtypes in ACTIB (study four) aims

Study four aimed to validate the findings from study three in a larger sample with larger power to detect differences. It was hypothesised that cognitions and behaviours would differ between subtypes. Based on the results from study three, the three specific hypotheses were that (1) unhelpful cognitions would be greater in those with IBS-D than IBS-C (2) unhelpful avoidance behaviours would be greater in those with IBS-D and IBS-A compared to IBS-C (3) control behaviours would not significantly differ across subtypes.

9.3.2 Summary and integration of study three and four results

Both studies found that subtypes IBS-D and IBS-A had significantly higher levels of avoidance behaviour than IBS-C. The findings regarding association of safety behaviours and bowel pattern subtype differed slightly across the two studies. Both studies found that those with IBS-A had higher levels of safety behaviours than those with IBS-D. Only study four found that individuals with IBS-C had significantly higher levels of safety behaviours than those with IBS-D also. The non-significant trend for a greater level of unhelpful GI related cognitions in IBS-D than IBS-C found in study three, became significant in study four. Study three found a significantly higher proportion of those with IBS-A with abdominal pain, than those with IBS-C or IBS-D.

9.3.3 Discussing the results

9.3.3.1 Increased avoidance in IBS-A and IBS-D

A potential reason for increased avoidance in IBS-A and D compared to IBS-C was postulated in chapters seven and eight to be due to the nature of the bowel symptom of diarrhoea, experienced by both subtypes. This symptom has been shown to be of primary concern to both subtypes in a recent study aimed at developing a subtype specific symptom severity measure for IBS (Fehnel et al., 2017). Concept elicitation interviews were used to identify the relative importance of symptoms as varied by subtype. Those with IBS-D and IBS-A identified the same symptoms most important to treat. These were the bowel symptoms of urgency and loose, watery stools and the abdominal symptoms of abdominal pain and cramping. The urgency associated with diarrhoea in IBS has been described as unpredictable, causing uncertainty and the use of avoidant behaviour strategies (Drossman et al., 2009; Rønnevig, Vandvik, & Bergbom, 2009; Drossman et al., 2011; Håkanson, 2014).

9.3.3.2 Increased use of safety behaviours

Those with IBS-A engaged in increased safety behaviours in both studies. Those with IBS-C also engaged in more safety behaviours in study four only, perhaps due to power. However, the post hoc power calculations (appendix G) indicated that the two studies had similar power to detect differences on this subscale (>0.9). It should be noted that there are issues with post hoc power calculations that can make them unreliable (Levine & Ensom, 2001). Nevertheless, the findings may also be due to the different participant samples; study four used individuals with refractory IBS, whereas this was not an inclusion requirement for study three. Individuals with refractory IBS-C will have had a longer duration of symptoms, which have not substantially improved after the use of first line medications. The lack of reprieve from symptoms over a long period may result in individuals becoming reliant on particular behaviours (such as stool checking or avoiding certain foods) to ease anxieties about the eventualities of not performing such behaviours (Thwaites & Freeston, 2005; Olatunji, Etzel, Tomarken, Ciesielski, & Deacon, 2011). The manifestation of safety behaviours in IBS generally, and specifically in IBS-C has been identified in the qualitative literature also (Casiday et al., 2008; Rønnevig et al., 2009; Håkanson, 2014). It remains unclear from the existing literature and from studies three and four, whether safety behaviours are generally heightened in IBS-C, or only in individuals with refractory IBS-C. Further studies are necessary to assess this.

Given the increased use of safety behaviours in IBS-C found in study four, and the increased use of avoidance behaviours in IBS-D found in both studies, the finding that those with IBS-A had higher levels of both types of unhelpful behaviour may be understood as a response to both diarrhoea and constipation symptoms. In IBS-A the fluctuations between bowel habits are rapid, with short symptom flare-ups and remissions (Tillisch et al., 2005). Traditional management approaches to IBS bowel symptoms involve the use of fibre supplements and laxatives to treat symptoms of constipation, and the use of antidiarrhoeal agents to treat diarrhoea symptoms. For individuals with IBS-A this approach may exacerbate symptoms, increasing frequency and severity of symptom fluctuations (Tillisch et al., 2005). Such issues regarding medication could explain the reliance on the use of avoidance and safety behaviours.

Another factor that may account for the differences found in behaviours across the subtypes is measurement error. It is a possibility that more items on the avoidance subscale of the BRQ may be relevant to the experience of diarrhoea, while more items on the safety subscale may be relevant to the experience of constipation. This could account for all of the behavioural differences found across the subtypes. This highlights the need to validate the BRQ within each IBS bowel pattern subtype.

9.3.3.3 More unhelpful GI related cognitions in IBS-D

The increased power to detect effects in study four compared to study three is likely to account for why the non-significant trend towards higher levels of GI-related cognitions in IBS-D compared to IBS-C in study three became significant in study four (appendix G). Factors such as unpredictability and increased burden associated with diarrhoea could explain this finding.

As with the BRQ, there is the possibility that measurement bias in the CS-FBD accounts for the findings. There may be more items in the scale that are relevant to those with IBS-D than they are to the other two subtypes. The validity of this scale for the different subtypes would need to be assessed before drawing further conclusions.

9.3.4 Clinical and research implications

9.3.4.1 Tailoring interventions

The results of studies three and four suggest that individuals with different IBS subtypes may have different cognitive and behavioural experiences. These results could provide a basis for the tailoring of psychological treatments in IBS. An area where the tailoring of

psychological treatments is important, is in the development of online interventions (Lustria, Cortese, Noar, & Glueckauf, 2009) such as the one developed in the ACTIB study (2.3, appendices E & H). Online interventions include interactive features that can guide users down specific paths, based on their responses to particular questions (Noar, Benac, & Harris, 2007; Lustria et al., 2009). For example, questions identifying predominant bowel pattern may funnel participants to information and activities tailored towards their particular cognitive and behavioural experiences. Techniques for IBS A and D may focus on reducing avoidance behaviours, whereas those with IBS-C may receive guidance in limiting the use of safety behaviours.

Membership of IBS subtypes fluctuates (Palsson, Baggish, Turner, & Whitehead, 2012). This could have implications for treatment development procedures. This is because should individuals receive a treatment course that has been tailored to their IBS subtype, subsequent change to the subtype may render the treatment no longer effective or appropriate. Treatments tailored to the IBS subtypes therefore need to be flexible to account for fluctuations in symptoms. Nevertheless, research generally suggests that from month to month subtypes remain stable (Engsbro, Simren, & Bytzer, 2012; Palsson et al., 2012). There are alternative methodologies that can assess the extent to which daily fluctuations of unique characteristics (such as bowel patterns) predict treatment response (Holmes et al., 2018). These methodologies include 'ecological momentary assessment', latent growth curve modelling and machine learning techniques (Holmes et al., 2018). Research utilising these methods could inform the extent to which bowel pattern subtype fluctuations impact on tailored treatment.

Should it be determined that subtype fluctuations do affect treatment response, flexible formulation-based treatment could be used to facilitate continued treatment response (Toner, 2005; Persons, 2012). This is intuitively sensible as treatment is based on the specific experiences of patients who experience symptom fluctuations, which are experienced with regularity and significance over the course of treatment. Using principles from personalised treatment approaches, a clinician can apply the general IBS CBT protocol transdiagnostically (across bowel pattern subtypes) and utilise information regarding predominant bowel pattern subtype to tailor particular aspects of the programme where appropriate (Thompson-Hollands, Sauer-Zavala, & Barlow, 2014).

9.3.4.2 Increasing the multidimensionality of subgroups in IBS

Research in IBS increasingly suggests the importance of increasing the multidimensionality of subgroups in order to create more clinically meaningful symptom profiles (Whitehead, Palsson, & Jones, 2002; Riedl et al., 2008; Polster et al., 2017). These studies have all indicated that the characterisation of bowel pattern predominance remains important but only when considered in addition to other factors such as somatic and psychological comorbidity (Whitehead et al., 2002; Riedl et al., 2008; Polster et al., 2017). Our study supports the suggestion that bowel pattern subtypes are important. The suggestion that cognitive and behavioural variables are also important factors for the characterisation of subgroups is novel. It concurs with the new characterisation of somatic symptom disorders in DSM-V (Association, 2013), where the importance of cognitive and behavioural responses have been highlighted. Subgroups identified using such variables may have the ability to further account for heterogeneity in IBS outcomes (e.g. symptom severity/QoL) and treatment outcomes.

9.3.4.3 Investigation of measurement bias

The results of studies three and four may indicate some measurement bias in relation to both the BRQ (Reme et al, 2010) and the CS-FBD (Toner et al, 1998) when applied across IBS subtypes (as discussed in 9.3.3.2 and 9.3.3.3). Therefore an important avenue for further investigation is the validity of these measures in different bowel pattern predominant samples.

9.4 Overall Strengths & Limitations

The specific strengths and limitations for each study are discussed in the respective chapters. Discussion here will focus on general issues arising across the studies and how the studies relate to each other.

9.4.1 Mediation studies

While narrow in the treatments included in the systematic review, the advantage was that the findings were more specific to CBT. This reduced potential ambiguities that could have arisen in the context of a mix of heterogeneous treatments. The disadvantage of only having mediation results from CBT studies was that inferences about mediators of other psychological approaches to IBS could not be made. As such the degree to which there are shared mechanisms across treatments remains unclear.

Although there were a limited amount of studies included in the review limiting the inferences that could be made regarding treatment mechanisms, the review provided an additional important contribution to the literature. It highlighted the disparity in the methods used for assessing mediation within the same field of research. The development of a clear set of quality assessment criteria (chapter 4, mediation quality assessment) aimed to remedy this by identifying standards future mediation research should adhere to. These criteria were used to guide the mediation analysis conducted in study two, substantially enhancing the methodological quality. Study two consequently ensured that (1) mediators and outcomes were temporally sequenced to allow causal inferences (2) analysis controlled for potential confounding effects of baseline mediator and outcome measures (3) multiple assessment of fit criteria were used for model fit (4) confidence intervals and path coefficients of indirect effects were reported (5) paths modelled were informed by theory, namely the three system's model.

There was however a limit to the extent to which study one could inform the design of study two as study two used data that had already been collected. Should there have been more flexibility in the design of study two, it would have been useful to include a measure of GSA in order to assess it as a mediator. This would also have allowed further analysis to explore the relationship between the constructs of GSA and general anxiety. Analysis such as principle component analysis could identify whether the two constructs overlap or are distinct (Abdi & Williams, 2010).

Future mediation studies could utilise both specific and general measures of psychological constructs to assess their relative importance. The illness perception questionnaire could be used as a general mediator.

Finally, a strength of study two was that it appeared to have sufficient power (.80) to detect mediation in the simple mediation models based on the post hoc guidelines developed by Fritz & MacKinnon, (2007). This is because all effect sizes of α and β paths were >.26 - with the exception of avoidance behaviour which fell just below it - and there was a sample size of 148 (see 2.4.2.2 and chapter 5, table 2). However, it is unclear whether there was sufficient power to detect sequential mediation effects, as there is not currently sufficient information on how to calculate power for more complex mediation models (Thoemmes, MacKinnon, & Reiser, 2010).

9.4.2 Subtype studies

A success of the two studies assessing subtype associations with various outcome variables was the partial replication of findings from study three in study four, suggestive of external validity (Francis, 2012; Makel, Plucker, & Hegarty, 2012). This is despite the fact that there were differences in the participant samples. Differences included the diagnostic criteria used to recruit participants and the exclusion of non-refractory IBS in study four. Participants in study three had to meet the Rome I criteria whereas participants in study four had to meet the Rome III criteria. It has been suggested that the Rome criterion have become more restrictive (Chey et al., 2002; Drossman & Dumitrascu, 2006; Dang, Ardila‐Hani, Amichai, Chua, & Pimentel, 2012) and therefore the two different studies may include slightly different subsections of the IBS population. This may also be likely due to the refractory nature of the IBS population in study four. Nevertheless both samples had similar baseline characteristics (chapters seven and eight). This may indicate that inclusion criteria differences did not contribute to difference in the two samples.

Due to the use of different diagnostic criteria, the studies also employed different methods of assigning bowel pattern subtype classifications making comparison difficult. However the classification methods were chosen to ensure they were as similar as possible. The same number of parameters were used to inform classification, with similar rating scales (Likert scale of 4 in study three and 5 in study four). The predominant difference between the two methods was the wording. For example participants were asked to rate frequency of either ‘diarrhoea’ and ‘constipation’ or ‘loose and watery stools’ and ‘hard and lumpy stools’.

Both studies may have been underpowered to detect differences across all outcome measures other than behaviours based on post hoc power calculations (appendix G). This could account for the lack of differences found on all of the other measures assessed. Power achieved for detecting behavioural differences was excellent however (>.80), which provides a certain degree of confidence in the findings that these differed across subtypes. However, as raised previously in the discussion and the respective chapters, there was the potential of measurement bias in the cognitive and behavioural measures. This limits the extent to which interpretations about the findings can be made.

Both studies were novel, providing important contributions to the field of research. Although the importance of cognitive and behavioural factors are discussed throughout the IBS literature (Creed & Guthrie, 1987; Drossman, Camilleri, Mayer, & Whitehead,

2002; Kennedy et al., 2012), very few studies have assessed cognitive differences between IBS subtypes. Those that have did not find significant differences between subtypes (Sugaya & Nomura, 2008; Stengel et al., 2010; Thijssen et al., 2010). The studies conducted in this thesis also appear to be the first studies to assess differences in GI related avoidance and safety behaviours across subtypes.

There are issues with comparison of findings across studies using different samples that are not matched. In studies three and four the diagnostic criteria for IBS differed. Theoretically this could mean that the samples represent different patient groups. Studies have shown that there are differences in the sensitivity of the various IBS diagnostic criteria (Ersryd, Posserud, Abrahamsson, & Simren, 2007; Sperber, Shvartzman, Friger, & Fich, 2007; Park et al., 2010). As such, the comparison of similarities and differences in findings from the samples of the two studies may not be attributable to the independent variables of interest (i.e. subtypes). There are additional potential confounders arising from two non-matched datasets that reduce the validity of comparisons between them. These confounders include but are not limited to the following factors: differential diagnostic criteria, age ranges, level of baseline affect, comorbidity and symptom duration.

9.4.3 Why assess mediators and subtype associations in one thesis?

This thesis seeks to combine understanding of subtype associations and therapeutic processes. Although not necessarily natural bedfellows the former can help contribute to the planning of the latter. Moderated mediation has been conducted by previous researchers in IBS (Labus et al., 2013). Moderated mediation detects where a mediated effect (e.g. cognitions) is different at different values of the moderator (e.g. bowel pattern subtype) (Mackinnon, Fairchild, & Fritz, 2007; MacKinnon, 2011). In the previous study by Labus et al (2013), the rationale for stratifying mediation analysis by baseline levels of QoL was not theoretically or empirically informed. The combined findings from this thesis however could inform the basis of such analysis. As the mediation studies indicate the importance of cognitions, behaviours and anxiety, these could be included as mediators in analysis. The findings from the two other studies suggest that subtypes (i.e. IBS-A, D or C) could moderate the extent to which such mediator variables produce change in outcome. Therefore future studies with sufficient power could apply moderated mediation analysis in this way.

9.4.4 Issues with the Rome Criteria

Although the Rome Criteria are widely adopted in IBS research, as previously discussed in the introduction (section 1.1, 1.8), it is used far less in the clinical diagnosis of IBS. This has implications for findings of research conducted in this thesis and more generally. Some studies have demonstrated poor validity of the Rome criteria in samples of patients with IBS as diagnosed by doctors (Dang, Ardila-Hani, Amichai, Chua, & Pimentel, 2012; Moayyedi et al., 2017; Mujagic et al., 2017; Chang et al., 2018). This may suggest that a proportion of patients diagnosed with IBS using methods alternative to that of the Rome criteria, may be precluded from IBS research. This may bias the results of such research, which may not be generalizable to all individuals with IBS in the general population.

The use of diagnostic criteria that does not have standardised implementation in clinical practice is not exclusive to IBS. This is an issue in functional bladder syndromes such as interstitial cystitis and bladder pain syndrome also. Multiple criteria have been developed as in IBS, with a lack of consensus regarding which should be the primary method of diagnosis (van de Merwe et al., 2008; Hanno et al., 2011). As such there is poor adoption of such criteria in clinical practice and physicians generally rely on diagnosis by exclusion (Hanno et al., 2011). This results in similar uncertain prognoses and treatment trajectories for these patients (Hanno et al., 2011). Although it is good practice to rule out other potentially harmful disease diagnoses, the patient journey would be enhanced with clear protocols for diagnosis.

9.4.5 The Effect of Comorbidities

Studies show that both somatic and affective comorbidities have a substantial negative impact on the experience of IBS (Lackner et al., 2014; Vu et al., 2014). This may be due to the increased stress caused by such factors (Chang, 2011), physiological sensitisation (Van Oudenhove et al., 2016) or lower resilience to cope with the burden of multiple symptoms and negative experiences (Johnston et al., 2015; Jason, Carr, Washington, Hilliard, & Mingo, 2017). We did not have data from the studies in the present thesis to assess the potential affect of somatic comorbidities. With regards to the subtype studies, previous studies have demonstrated that the presence of somatic and affective comorbidities is a defining element of more multidimensional subgroups in IBS (Polster et al, 2017). Future studies should therefore aim to include this data in analysis assessing IBS subtypes.

The subtype studies did however assess whether anxiety and depression were differentially associated with the IBS subtypes. The findings as discussed previously, suggested that neither anxiety nor depression had a differential association between the subtypes. However, level of anxiety and depression were not controlled for in the ANOVAs. This means we cannot be certain that anxiety or depression accounted for the influence of subtypes on differences in avoidance and control behaviour or GI related cognitions. Although this is unlikely to have changed the results judging by the existing findings and the descriptive data at baseline, it is something that should perhaps be explored in future studies.

In the mediation study, anxiety was controlled for in the sequential mediation models. This means that the potential effect of baseline anxiety was accounted for in the mediation models. The significant mediation pathways found therefore apply to individuals with low, moderate and high baseline anxiety. Depression, however, was not controlled for. The sample generally had low to moderate HADS depression scores suggesting that it's probably unlikely that level of depression in our present sample would affect the findings. Nevertheless, it could be included as a covariate in future studies. A previous study demonstrated that low baseline QoL moderated mediation (Labus et al, 2013). Specifically, anxiety and cognitions were only found to mediate treatment effect of CBT on symptom severity, when baseline QoL was low. Although low baseline QoL is not a comorbidity, this demonstrates how baseline factors such as high comorbidity can affect mechanistic processes.

9.4.6 Alternative approaches

This thesis aimed to explore cognitive and behavioural factors in IBS. However, there are limitations to CBT generally and with specific application to IBS. A key consideration when interpreting results from CBT research is the extent to which patients remained adherent and within treatment. There is variation in adherence of between 20% and 50% in CBT (Bados, Balaguer, & Saldaña, 2007). This raises important questions regarding who makes use of CBT therapy. Such variability may suggest that CBT is only potentially effective for a self-selecting sample. There are also issues regarding the time-limited nature of CBT, particularly within stepped care services (Williams & Martinez, 2008). While for some patients a finite amount of specified sessions may be sufficient to induce change and positive outcomes, for others with more complex needs, it may be inadequate (Williams & Martinez, 2008). In IBS, there is a high prevalence of early life adverse events including sexual abuse (Bradford

et al, 2012). This can increase the complexity of the case, which may require more intensive treatment.

It could be argued that CBT does not elucidate all of the potentially important targets for change (House & Loewenthal, 2008; Smith, 2017). There is an increasing focus on the mechanisms posited by therapeutic processes implicated in ACT (Smith, 2017). Key processes in ACT include cognitive defusion, acceptance and the use of value-based goals (Arch & Craske, 2008; Bravo Ferreira et al., 2011). Defusion refers to the process of gathering distance from thoughts or '*decentring*' as practiced in mindfulness. Acceptance, rather than passive resignation is an intentional lowering of resistance to particular experiences. The focus on value-based goals allows clients to identify positive courses of action that are in line with these goals. Although these treatment targets may seem distinct from CBT, it could be argued that only the treatment *procedures* rather than the treatment *targets* are distinct (see section 9.4.8)(Arch & Craske, 2008). For example, both CBT and ACT target the reduction of avoidance and reduce the impact of unhelpful cognitions. The distinction lies in the employment of different treatment techniques to do so (Arch & Craske, 2008; Smith, 2017).

The studies in the present thesis focussed on the key processes and mechanisms identified in the cognitive behavioural model of IBS. This left other potential mechanistic processes identified by treatment models such as ACT unexplored. The systematic review in chapter 4 aimed to assess mechanisms of psychological treatment for IBS more broadly. However there were limited mediation studies conducted outside the context of CBT treatment. As such, it is difficult to make conclusions regarding other potential mechanisms of treatment effect, or key mechanisms that should be targeted in treatments going forward. More mechanistic studies are needed in the context of other treatment approaches in IBS. Ideally these should utilise robust methodologies as described in the guidelines developed in chapters three and four, to standardise assessment. These guidelines are in line with a recent Lancet Psychiatry commissioned report on psychological treatment development (Holmes et al, 2018)

9.4.7 Terminology

9.4.7.1 Terms to depict intervention 'intensity'

In the ACTIB study, there were two treatment conditions. The main difference between conditions were the format of the intervention (web or paper manual) and the number and duration of sessions with a therapist over the phone (section 2.3.1). Both treatments

may therefore be categorised as ‘low intensity’ in the traditional sense of the word (Haaga, 2000; Bennett-Levy et al., 2010) as they consisted of a limited number of sessions, remotely accessed. However, a key distinguishing factor of the interventions provided in ACTIB, was that all of the therapists delivering treatment were highly experienced with a minimum of eight years treating long-term conditions with CBT. Rather than conceptualising treatments as high versus low intensity, it may be more appropriate to consider them in terms of ‘guided self-help’ or ‘guided self-management’. Such terms more accurately depict the treatments provided in the ACTIB trial.

9.4.7.2 ‘Safety behaviour’

The term ‘safety behaviour’ was used in this thesis to refer to a particular type of behavioural response to IBS symptoms. The rationale for considering this subset of behavioural response as separate to avoidance behaviours, was that the BRQ had two subscales distinguishing between them (Reme at el, 2010). In the scale developed by Reme et al (2010) however, ‘safety behaviours’ were referred to as ‘control behaviours’ depicting behaviours in which individuals attempted to exert control over their symptoms. This included items such as excessive straining or the carrying of extra items in case of an accident. It may be that neither of the terms ‘safety’ or ‘control’ behaviour are appropriate. It has been suggested that particular actions that may get conceptualised as safety behaviours are in fact facilitative of positive adjustment/action and are not preventative of disconfirmatory experiences (Rachman, Radomsky, & Shafran, 2008; Rachman, Shafran, Radomsky, & Zysk, 2011). It is suggested that some of these behaviours may be adaptive rather than inhibiting. Reference to maladaptive behavioural responses to symptoms in IBS may instead be better referred to as ‘unhelpful illness related behaviour’. In the context of this thesis, this term has been used to identify both avoidance and control behaviours collectively. Terminology for ‘control’ behaviours specifically, could also be changed to ‘unhelpful illness related *control* behaviours’.

9.4.8 The Role of Mediation Analyses in the Development of Treatments

The utility of mediation analysis in informing the development of treatments has been discussed in chapter 3 and in relation to the findings for studies one and two. Such discussions have focussed on the importance of mediation analysis however, it is also important to contextualise it amongst the other important components of treatment development. It has been argued that treatment development research and processes, particularly within CBT, has focussed on treatment *targets* rather than *procedures* (Clark, 2004). For example focus has been on the therapeutic targets of change such as

unhelpful cognitions and behaviours, with less focus on the techniques (procedures) involved in changing these factors. Teasing therapy *targets* apart from therapeutic *procedures* can be hard to conceptualise. Different methodology is used to assess the utility of each. Mediation analysis can be used to assess the efficacy of therapy targets. This is conducted more commonly than research investigating the efficacy of treatment procedures. Clark et al (2004) suggest that procedures may be tested using 'decomposition studies'. These include comparison of the efficacy of the 'full treatment' to the treatment minus a particular procedure. For example, the efficacy of CBT may be assessed in its full form and then compared to CBT minus exposure techniques.

The procedures employed in psychological treatment are arguably key in ensuring the targets are effectively changed. As previously discussed, theoretical models can be used to identify treatment targets (chapter 3), however, there are additional key processes involved in treatment development. This is especially the case where treatment protocols are being adapted for different conditions. Key processes involved in treatment development include (1) conducting interviews with the target patient population to identify core factors to be changed and/or accounted for in treatment (2) formulation regarding why and how such factors occur, with consideration of relevant theory/ies (3) experimental studies assessing hypotheses formed in formulations (4) development of treatments, with procedures aiming to address the identified factors of importance (5) RCTs assessing the efficacy of such treatments (Clark, 2004; Holmes et al., 2018). Assessment of mechanisms using mediation analysis can occur at multiple points within this process to refine hypotheses and treatment design.

9.5 Conclusions

The studies in this thesis demonstrate the importance of cognitive and behavioural factors in irritable bowel syndrome. Both mediation studies suggest that it is important to target GI related cognitions and behaviours in psychological treatment for IBS. Cognitive and behavioural factors also appear to be important in the distinction between IBS bowel pattern subtypes. Treatment could be targeted to specific responses.

9.6 Future Research and Implementation Directions

Two future research directions relate to potential measurement issues arising in the present thesis. The BRQ and CS-FBD should be validated in the context of each IBS bowel pattern subtype. This would ensure that items relate equally across the different

symptom experiences (i.e. constipation, diarrhoea or alternation of them both). Furthermore, the relationship between GSA and general anxiety could be examined.

Ideally the analysis in study two should be replicated in a larger sample. This would determine whether avoidance behaviour was a significant mediator in a study with sufficient power. In addition future mediation studies might include assessment of GSA, as indicated by study one. Another important aspect that future mediation studies may address is whether adding directionality to mediation models improves the fit of the models to the data. Alternative modelling would involve assessing parallel process mediation models, whereby the role of all mediators included in the models are assessed concurrently. Such analysis would indicate whether cognitive, behavioural and affective processes work in parallel to produce change in outcomes or whether change between mediators is sequential. Parallel mediation models can also identify where a variable identified as a significant mediator in a simple mediation model becomes insignificant when included in a multiple mediation model.

With regards to subtypes in IBS, the next step would be to identify more multi-dimensionally defined subgroups in IBS. Cluster analysis is a statistical method that can be used to achieve this. It involves using multiple measures as informed by theory and research to form 'clusters' (i.e. subgroups) that are characterised by the particular variables. Based on the existing evidence, recommendations and the studies included in the thesis, it would be important to include bowel pattern subtypes, measures of GI related cognitions, behaviours, psychological and somatic comorbidities. The identification of multidimensional subgroups could help to inform future developments of the Rome diagnostic criteria to enhance the provision of positive diagnoses (Spiegel, Farid, Esrailian, Talley, & Chang, 2010).

Subgroups could also be included in moderation analysis to assess whether particular subgroups have different responses to particular treatments. There is scope for this analysis to be conducted in the context of data set 2.

Finally, to combine insights gained from all of the studies conducted in the thesis, future research may use moderated mediation. This would involve assessing whether either bowel pattern subtype or more multidimensional subgroups in IBS, moderate the mediated effect of cognitions, behaviours and/or anxiety. All of the future suggestions for research would contribute to an empirical basis for personalising treatments and modifying treatment approaches. In terms of implementing insights from such research, frameworks such as intervention mapping (Bartholomew, Parcel, & Kok, 1998) and the

Medical Research Council guidelines for the development of complex interventions (Craig et al., 2008) can be used. These guide the process of identifying relevant aspects from theory and empirical research to inform the design of future interventions.

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Appendices

Appendix A

Ethical Approval

NHS
Health Research Authority

NRES Committee South Central - Berkshire
Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 3421389
Facsimile: 0117 3420445

11 June 2013

Dr Hazel Everitt
Clinical Lecturer in General Practice
University of Southampton
University of Southampton
Aldermoor Health Centre, Aldermoor Close
Southampton
SO16 5ST

Dear Dr Everitt,

Study title: **ACTIB: (Assessing Cognitive behavioural Therapy in Irritable Bowel): A randomised controlled trial of clinical and cost effectiveness of therapist delivered cognitive behavioural therapy and web-based self-management in irritable bowel syndrome**
REC reference: **13/SC/0206**
Protocol number: **5334**
IRAS project ID: **125700**

Thank you for your letter of 10 June 2013. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 03 June 2013

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Covering Letter		10 June 2013
Participant Consent Form	2.0	10 June 2013
Participant Information Sheet	2.0	10 June 2013

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Advertisement	ACTIB Recruitment Poster: Version 1	25 March 2013
Covering Letter		28 March 2013
Covering Letter		10 June 2013
Evidence of insurance or indemnity	Miller Insurance	01 August 2012
GP/Consultant Information Sheets	NICE Guidance on IBS: Version 61	01 February 2008
GP/Consultant Information Sheets	Letter to Inform the GP/Consultant of Patient Participation	13 March 2013
Interview Schedules/Topic Guides	ACTIB Topic Guide 3 Month: Version 1	25 March 2013
Interview Schedules/Topic Guides	ACTIB Topic Guide 12 Month: Version 1	25 March 2013
Investigator CV	Dr Everitt	28 March 2013

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

13/SC/0206	Please quote this number on all correspondence

Yours sincerely,

Ms Rae Granville
Committee Co-ordinator

E-mail: nrescommittee.southcentral-berkshire@nhs.net

Copy to: *Dr Martina Prude*

NHS
National Institute for Health Research

Clinical Research Network
South London

16th Floor, Tower Wing
Guys Hospital
Great Maze Pond
London, SE1 9RT

Tel: 020 7188 0494
Email: crnsouthlondon@gstt.nhs.uk
Web: www.crn.nihr.ac.uk/slondon

Dr Hazel Everitt
Clinical Lecturer in General Practice
University of Southampton
Aldermoor Health Centre, Aldermoor Close
Southampton SO16 5ST

Date reissued: 06 May 2015
(Original letter dated: 11 June 2014)

Dear Dr Everitt

Study title: ACTIB (Assessing cognitive behavioural therapy in irritable bowel): A randomised controlled trial of clinical and cost effectiveness of therapist delivered cognitive behavioural therapy and web-based self-management in irritable bowel syndrome
REC Ref: 13/SC/0206
CSP/R&D Ref: 125700

NHS Research Governance (RG) assurance for the above research has been given for all **CCG's within London South CRN**. The activities described in the application form and supporting documentation approved by an NHS Research Ethics Committee (REC), subject to the conditions listed below and overleaf. RG assurance is given on the understanding that the study is conducted in accordance with the Research Governance Framework. RG assurance covers the sites listed above.

The study team must get written agreement from each participating site confirming their decision to take part in this study. Please give a copy of this letter to each participating site.

Please note that one of the DH/NIHR objectives for UKCRN portfolio projects is for the first patient to be recruited within 30 days of the date of this letter. A CRN: South London Research Officer will be working closely with the study team to enable this objective to be achieved. If you have any queries about this please contact Simon Davies at Simon.Davies@gstt.nhs.uk

If you require any further information or advice, do not hesitate to Clare Gillott.

NHS
National Institute for Health Research

Clinical Research Network
South London

16th Floor, Tower Wing
Guys Hospital
Great Maze Pond
London, SE1 9RT

Tel: 020 7188 0494
Email: crnsouthlondon@gstt.nhs.uk
Web: www.crn.nihr.ac.uk/slondon

Yours sincerely,

Clare Gillott
Industry & RM&G Operations Manager

c.c. Mr Simon Davies, CRN: South London

Research Governance assurance is given subject to the following conditions:

There will be no call upon NHS resources other than any mentioned in the application and agreed with the R&D Office and the Primary Care site.

The research sponsor or the CI or the local PI at the research site may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. The R&D Office should be notified if any such measures have been taken. The notification should also include the reasons why the measures were taken and the plan for further action. The R&D office should be notified within the same time frame as the REC.

The Sponsor organisation must have in place procedures for detecting and dealing with misconduct and fraud. All researchers must be aware of these procedures and any instances must be reported to the R&D Team.

Unless the Study Team requests otherwise, we will include details of this project on the Primary Care database.

We will ask the Study Team to send us a copy of the final report and/or a summary of the findings.

Delivering research to make patients, and the NHS, better

NHS
National Institute for Health Research

Clinical Research Network
South London

16th Floor, Tower Wing
Guys Hospital
Great Maze Pond
London, SE1 9RT

Tel: 020 7188 0494
Email: crnsouthlondon@gstt.nhs.uk
Web: www.crn.nihr.ac.uk/slondon

Only members of the clinical care team can access patient identifiable information without the patient's consent. Researchers are not part of the clinical care team and therefore require a patient's consent for access to their confidential data.

You must comply with the site information governance (IG) requirements.

GP indemnity for routine clinical practice is covered by GP Medical Defence Union arrangements.

All primary care recruitment must be uploaded to the NIHR portfolio by the study team.

Optional

The research must not start until letters of access have been issued and we will write to the study team separately about this.

For a CTIMP trial, the PI must have attended a Good Clinical Practice study day within the past 2 years.

Please note that Research Service Support Costs associated with this study will need to be agreed separately. Please contact Jo Burns, Research Delivery Manager at Jo.Burns@gstt.nhs.uk if this has not yet been done.

Appendix B

Recruitment invite letter and participant information sheet

NHS
Lambeth
Clinical Commissioning Group

Participant Information Sheet

ACTIB (Assessing Cognitive behavioural Therapy in Irritable Bowel): A randomised controlled trial of clinical and cost effectivensss of therapist delivered cognitive behavioural therapy and web-based self-management in irritable bowel syndrome

Chief Investigator: Dr Hazel Everitt, Clinical Lecturer in General Practice, University of Southampton

Please read this information carefully before deciding to take part in this project. If you are happy to participate please return the reply slip in the FREEPOST envelope that is enclosed with this letter.

What is the project about?
We are a group of researchers based at the Department of Primary Medical Care at the University of Southampton and the Institute of Psychiatry, at King's College London undertaking studies into the management of Irritable Bowel Syndrome (IBS)

Why have I been chosen?
You have received this letter because you have consulted your GP in the last 12 months about IBS or you are currently seeing a consultant about your symptoms.

Do I have to take part?
Participation in the project is entirely voluntary. It is up to you to decide whether to take part. You are able to withdraw at any time without giving a reason. If you decide to withdraw or not to take part in this study this will not affect the standard of care you receive.

What will happen to me if I take part?
If you decide you would like to take part we would ask you to return the reply slip at the bottom of the attached letter to the study team. You can also email them directly or contact them by phone using the details at the end of this sheet.

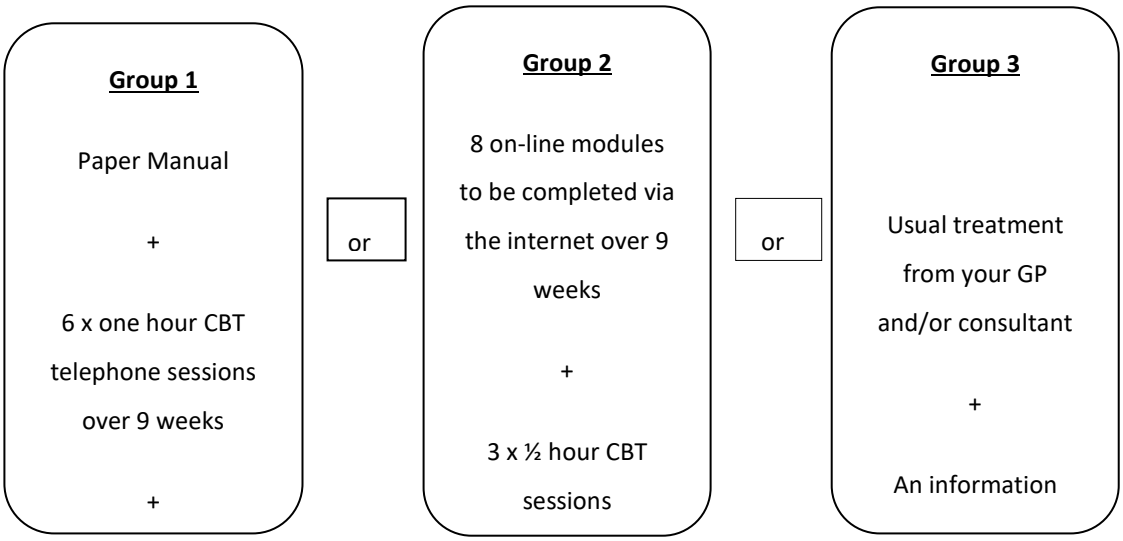
A member of the team will then go through some questions with you to make sure that you are suitable to take part in the study. If you are eligible to take part you will then be asked to have a blood test to make sure you are not anaemic and that there are no signs that your bowel symptoms are due to other illnesses.

The blood test is a straightforward, safe procedure but may cause some minor discomfort and you may notice some slight bruising which should subside in a couple of days. The blood will sent for analysis to the Pathology Laboratory at Southampton General Hospital.

As part of this study, you will continue to receive treatment as usual from your doctor as you normally do and can continue using any medication that you currently find helpful. However, you will also have the opportunity for additional treatment which has been shown to reduce IBS symptoms in previous studies. You won't be able to choose which treatment as a computer system will allocate you to one of three groups at random (see box diagram below for details). People in group 1 will receive a manual about managing their IBS as well as six one hour sessions with cognitive behavioural therapist (CBT) over the telephone over a 9 week period with two one hour extra telephone sessions at 4 and 8 months to see how they are doing. Sessions will be scheduled at times that suit you. We will endeavour to use the same therapists for you throughout your participation in the trial.

People in group 2 will have access to a self-management website for IBS consisting of 8 on-line modules to complete in their own time on the internet over 9 weeks. In addition, they will receive
three half hour support sessions with a CBT therapist over the telephone. These will be followed up with two half hour booster telephone sessions at 4 and 8 months to see how people are doing.

People in group three will initially just receive an extra information sheet about their conditions. However at the end of the study they will be given access to the IBS self-management website.



Both the therapy manual and the self-management on-line programme are designed to help you manage your IBS and consists of 8 sessions or 'modules' to work through over a nine week period. The website group (group 2) will do this largely on their own. Each module takes around 30-45 minutes to complete. The therapy group (group 1) will do this in conjunction with a therapist.

Examples of the type of material covered in the modules are:

Understanding your IBS symptoms

Assessing your symptoms,
Managing Symptoms and Eating, Exercise and Activity
The role of thoughts and emotions in IBS
Managing Stress and Sleep
Managing Flare-ups and
The Future.

During your participation of the study we will ask you to fill in an on-line questionnaire at the start and 3, 6 and 12 months to assess your IBS symptoms and ask you about how you are feeling and how you believe your quality of life is.

You will also be asked to keep a simple log of homework tasks to be completed.

At the end of the study, we will also check your GP notes to see how many appointments you have had for your IBS in the 12 months before you came into the study and for the 12 months that you will be part of the study.

We will also ask a small number of people who enter the study if they would like to take part in an interview which should last between 30 and 60 minutes about how it was taking part in the study and any useful feedback they can give us about the study. You will have the option to agree to this or not and it is entirely up to you to decide.

Are there any benefits in my taking part?
Previous studies suggest that your IBS symptoms will be helped by the therapist or the self-management programme, however we cannot guarantee change in your symptoms. Your information will help us gain more knowledge regarding the website programme and the therapist treatment used in the trial, the cost of each and whether we should offer either of these routinely to people with IBS.

Will my participation be confidential?
All information that you provide will be strictly confidential. You will be identified by an ID number and the information you provide will be stored in locked filing cabinets or a password protected computer. The study will fully comply with the Data Protection Act and University policy on conducting research studies.
Your GP will be informed that you are participating in the study, so that they are aware that you receiving additional support for your IBS. The self –management website is a secure website and any information you provide on the website is only accessible to you and select people in the research team.

Who is organising the funding?
The study is funded by the NHS as part of the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) funding stream.

Who is managing the study?
The study is being sponsored by the University of Southampton who will monitor the study regularly to make sure that everything is being done as agreed at the start. The Berkshire Research Ethics committee has reviewed the study and are happy for it to go ahead (Reference: 13/SC/0206).

What happens if something goes wrong?
If you have complaints about the way your illness was managed, this study will not affect your normal rights to pursue a complaint within the NHS in the normal way.

If you were to have any concern or complaint about this project you can contact the head of Research Governance at the University of Southampton – Dr Martina Prude,

University of Southampton, Highfield Campus, Southampton, SO17 1BJ Telephone: 023 8059 5058
email: mad4@soton.ac.uk

Where can I get more information?
If you have any questions about this research after reading this information sheet please contact Alice Sibelli and Sula Windgassen by telephone: 0207 188 0179 or email: actib_study@kcl.ac.uk

Practice Headed paper

<*patient name and address*>

<insert date>

ID <insert Study ID>

Dear <insert patient name>

ACTIB: Assessing Cognitive behavioural Therapy in Irritable Bowel

We are writing to invite you to take part in a study that is being led by researchers at the King's College London, University of Southampton and hosted by a number of different NHS trusts. You have been identified as a suitable participant for this study because you have consulted your GP or seen a consultant as you are suffering from IBS. Your participation in the study is purely voluntary and you may decide not to take part without affecting your care in any way.

We have enclosed an information sheet outlining the study, telling you more about it and what you would be asked to do should you decide to take part. This contains contact details if you require any further information. If you are interested in taking part, please complete page 2 of this letter and return it directly in the FREEPOST envelope enclosed.

When we receive your reply a member of the research team will contact you to assess whether or not you would be eligible to take part. Please note that if you have had access to the MIBS (Managing IBS study) website you would not be eligible to participate in this study.

If you do not want to participate or you are not eligible please complete page 3 of this letter and return it directly in the FREEPOST envelope enclosed.
Thank you very much for taking the time to read this letter and the attached information sheet.

Yours sincerely

Dr <insert GP name>

ID <insert Study ID>

If you wish to take part of our study please fill in the following sheet and send it back to us in the FREEPOST envelope.
I would like to take part in the IBS study and am happy for a researcher to contact me to discuss the study further *(please tick)* ☐

Patient Details Not To Be Entered on MACRO

My name is: ……..
I am male /female (please circle)
My date of birth is: ……
My Address is: ……
……..
……..
……..
Postcode…….
My contact telephone number is:
Home ……..
Mobile …….

My email address is……
(Please ensure you complete a current email address as we may contact you by email)
My GP is:
GP Name……
GP Surgery Address…….……..……
…….……..……..

……..……..
Signature ……
Date……

ID <insert Study ID>

If you do not wish to take part of our study, please fill in the following sheet and send it back to us in the FREEPOST envelope. Your responses will help us in the planning and design of future research studies. We truly appreciate your time. Thank you.
I do not wish to take part in this study because: ***(tick all that apply)***

1. I have had previous access to the MIBS (managing IBS study) website and thus am not eligible for this study ☐

2. I was involved in the MIBS study, and do not wish to participate ☐

3. I do not have time in my daily schedule ☐

4. I do not wish to take part in the telephone Cognitive Behavioural Therapy ☐

5. I do not wish to take part in the on-line self-management programme ☐

6. My IBS symptoms have improved and I do not currently need additional help ☐

7. Any of the previous options do not apply to me (please specify your own reasons below) ☐

_____
_____
_____
_____

Appendix C

Consent completed online

ONLINE CONSENT FORM

ACTIB (assessing Cognitive behavioural therapy in Irritable Bowel): A randomized controlled trial of clinical and cost effectiveness of therapist delivered cognitive behavioural therapy and web-based self-management in irritable bowel syndrome

Chief Investigator: Dr Hazel Everitt
Research team email address: actib@soton.ac.uk
Research team telephone number: 023 80241066
Patient ID:

Please tick the box(es) if you agree with the statement(s):

1.) I have read and understood the information sheet (dated ……., version no. …….) and have had the opportunity to ask questions about the study

yes no

2.) I agree to take part in this research project and agree for my data to be used for the purpose of this study.

yes no

3.) I understand that I may be contacted at a later date to take part in an interview about my experiences of being involved in the study.

yes no

4.) I understand that my GP notes will be accessed at the end of the study to gather data on GP consultations for IBS.

yes no

5.) I confirm that I am aware that if I am randomised to the therapist or low intensity CBT trial arm that the telephone sessions will be audio recorded.

yes no

6.) I understand that the data I provide may be monitored by a regulatory authority such as the University of Southampton or the NHS trust that is hosting the study.

yes no

7.) I understand my participation is voluntary and I may withdraw at any time without my legal rights being affected

yes no

8.) I agree to my GP being told about my participation in the study.

yes no

9.) I agree to being contacted in the future for any studies related to this one.

yes no

10.) I agree to have a blood test and for that sample to be analysed at the Pathology Laboratory at Southampton General Hospital.

○ yes ○ no

Appendix D
Questionnaires
Screening Questionnaire

ACTIB
Assessing Cognitive behavioural Therapy in Irritable Bowel

Screening Questionnaire

PT Invite ID [ ]

Instructions

Before you begin
Have the patient's reply slip to hand with contact details
Write the PT Invite ID on this questionnaire in the box at the top

Ring the patient as soon as you receive a positive reply from the invite letter. Make 3 attempts. If possible, one attempt should be out of working hours, or on a Saturday, or leave a message to ask the patient to ring you. If you do not reach the patient after 3 attempts, leave a message to ask them if there is a better number and note this for future calls. Note down here each time you call, e.g.
Attempt 1, date, time - no one home, left a message, etc.
Attempt 2, date, time - no one home etc.
Attempt 3 write - unable to contact patient.
Stop trying after 3 attempts.

Attempt	Date	Time	Outcome
Attempt 1			
Attempt 2			
Attempt 3			

If a patient answers a question that triggers exclusion, tick the box in the margin and say to the patient that actually you don't fulfil the criteria and thanks them very much for their interest.

Phone Call Script

Hello, my name is ……and I am calling on behalf of the ACTIB Study. We received your reply slip to say that you are interested. Thank you. Before you enter the study we would like to ask you a few questions to make sure that you fulfil the entry criteria and that you do not have any health problems to prevent you from participating. We will ask you some questions about your IBS symptoms and your general health. Your answers will help us to determine if you have the features of Irritable Bowel Syndrome that are required for participation in this study. Are you happy for me to continue?

All the information you give will be confidential. These questions should take around 15 minutes and we should be able to tell you straight away if you can be included in the study, subject to the results of a blood test. If you are eligible, we will inform your GP for safety reasons. If your answers to these questions show something should be investigated further we will inform you and your GP.

		Tick if an exclusion
	(circle)	
Have you received CBT for IBS in the last two years?	Yes / No	☐

If yes, please list what it was for and the type if known *(refer to TC and RMM to determine if an exclusion)*

……

Have you had previous access to the MIBS website?	Yes / No	☐
Are you currently participating in an IBS trial?	Yes / No	☐
Exclude if yes		

Before I start the questions can I confirm your contact details?

Name	……..…
Sex (circle)	male /female
Date of birth	……..……..
Address	……..……..
	…….
	…….
	…….
Postcode	……
Home Telephone	……
Mobile Telephone	……
Email	……
GP Name	……
GP Surgery	……
GP Surgery Address	……
	……

Section 1 About Your IBS

Tick if an exclusion

1.1 How long have you had IBS?
Exclude if less than 12 months

☐

☐ years ☐ months

1.2 When was your IBS first diagnosed?

☐☐☐ Ddmmyyyy

1.3 Have you been offered any of the following medications for your IBS, or any others not listed, (*please note the name*)?

☐

Exclude if no ticks

Type	Generic Name	Trade Name	Tick
Antispasmodics	Mebeverine	Colofac	
	Dicycloverine	Merbentyl	
	Hyoscine	Buscopan	
	Propantheline	Pro-Banthine	
	Alverine	Spasmonal	
	Atropine		
Antidepressants SSRI	Citalopram		
	Fluoxetine	Prozac	
	Escitalopram		
	Sertraline		
	Paroxetine	Lustral	
Antidepressants TCA	Amitriptyline		
	Nortriptyline		
	Imipramine		
	Iofepramine		
	Trazodone		
Fibre Based	Isaghula Husk	Fybogel	
		Regulan	
	Methylcellulose	Celevac	
	Sterculia	Normacol	

Section 2 About Your Symptoms (Rome III)

Tick if an exclusion

2.1 In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?

☐

Exclude if tick 0 or 1

0. Never	
1. Less than one day a month	
2. One day a month	
3. Two to three days a month	
4. One day a week	
5. More than one day a week	
6. Every day	

2.2 For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?

☐

Exclude if tick 1

0. No	
1. Yes	
2. Does not apply because I have had the change of life (menopause) or I am male	

2.3 Have you had this discomfort or pain 6 months or longer?

☐

Exclude if tick 1

0. Yes	
1. No	

2.4 How often did this discomfort or pain get better or stop after you had a bowel movement?

☐
☐

Exclude if tick 0, unless they answer 1 to 4 in either Q2.5 or Q2.6 AND they answer 1 to 4 in either Q2.7 or Q2.8
If tick more than 0 then they can be included if they answer either Q2.5 or Q2.6 as more than 0 OR either Q2.7 and Q2.8 as more than 0, otherwise exclude

0. Never or rarely	
1. Sometimes	
2. Often	
3. Most of the time	
4. Always	

2.5 When this discomfort or pain started, did you have more frequent bowel movements?

☐

Exclude if tick 0 AND Q2.6 tick 0; AND if they also answer 0 in both Q2.7 and Q2.8 regardless their answer in question 2.4

Tick if an exclusion

0. Never or rarely	
1. Sometimes	
2. Often	
3. Most of the time	
4. Always	

2.6 When this discomfort or pain started, did you have less frequent bowel movements?

Exclude if tick 0 or Q5 tick 0

0. Never or rarely	
1. Sometimes	
2. Often	
3. Most of the time	
4. Always	

2.7 When this discomfort or pain started, were your stools (bowel movements) looser?

Exclude if tick 0 or Q8 tick 0

0. Never or rarely	
1. Sometimes	
2. Often	
3. Most of the time	
4. Always	

2.8 When this discomfort or pain started, how often did you have harder stools?

Exclude if tick 0 or Q7 tick 0

0. Never or rarely	
1. Sometimes	
2. Often	
3. Most of the time	
4. Always	

2.9 In the last 3 months, how often did you have hard or lumpy stools?

No exclusion based on these

0. Never or rarely	
1. Sometimes	
2. Often	
3. Most of the time	
4. Always	

2.10 In the last 3 months, how often did you have loose, mushy or watery stools?

Tick if an exclusion

No exclusion based on these

0. Never or rarely	
1. Sometimes	
2. Often	
3. Most of the time	
4. Always	

Section 3 Final Questions

Exclude if any answer 'no'	
Adults (18yrs and over) with refractory IBS fulfilling ROME III criteria and who have been offered first-line therapies (e.g. antispasmodics, anti-depressants or fibre based medications) but still have continuing IBS symptoms for 12 months or more. If over 60 must have had a consultant review in the previous two years to confirm that their symptoms are related to IBS and that other serious bowel conditions have been excluded	
No unexplained rectal bleeding or weight loss*	
No inflammatory bowel disease	
No Coeliacs disease	
No peptic ulcer disease	
No colorectal carcinoma	
No speech or language difficulties	
Internet access	
No participation in the MIBS study	

**(patients who tick no to this question should be asked to see their GP to discuss their symptoms further and let them know that we will contact their GP also)*

That is the end of the questions. Do you have any questions/comments?

Next Steps

Proceed
Your answers indicate that you are eligible to take part in the study. Next, you will receive an email with instructions for completing an online consent form and once we get a notification when you have done that, we will email you the instruction for getting a blood test done.
Exclusion
The answers you gave us in the questionnaire indicate that you should not be included in this study. You will receive an email confirmation from us.

Thank you for your time in answering these questions and thank you again for participating in the ACTIB study.

ACTIB

Assessing Cognitive behavioural Therapy in Irritable Bowel

3 Month Questionnaire

Thank you for your continued participation and support for the ACTIB Study. It is now time to complete your 3 month questionnaire. This questionnaire is completely confidential and will only be seen by the researchers involved in the study.

Please try to complete all the questions even if they seem similar or repetitive as this will help us to collect the most reliable information for the study. Please enter the date completed below.

If you have any study related questions please get in touch by email: actibstudy@soton.ac.uk

Study ID | | |

Date Completed ddmmyyyy | | | | | | | | |

IBS symptom severity score (IBS-SSS) Questionnaire

About Your IBS

It is to be expected that your symptoms might vary over time, so please try and answer the questions based on how you currently feel (i.e. over the last 10 days or so).

1. a) Do you currently suffer from abdominal (tummy) pain? Yes No

b) If yes, how severe is your abdominal (tummy) pain? Please rate your pain from 0-100 using the scale below, and mark your answer on the line:

0% _____ 100%

No pain not very severe quite severe severe very severe

c) Please enter the number of days that you get the pain in every 10 days.

For example, if you enter 4 it means that you get pain 4 out of 10 days. If you get pain every day enter 10.

Number of days with pain ☐

2. a) Do you current suffer from abdominal distension* (bloating, swollen or tight tummy)?
*(*women please ignore distension related to your periods)*

Yes No

b) If yes, how severe is your abdominal distension/tightness? (mark your answer on the line):

0% _____ 100%

No distension not very severe quite severe severe very severe

3. How satisfied are you with your bowel habit? (mark your answer on the line):

0% _____ 100%

Very happy quite happy unhappy very unhappy

4. Please indicate on the line below how much your Irritable Bowel Syndrome is affecting or interfering with your life in general:

0% _____ 100%

Not at all not much quite a lot completely

Work and social adjustment scale (WSAS) questionnaire

We would like to find out more about how your IBS impacts on your daily life. Please circle the number that applies to you.

Because of my IBS my ability to go to work or attend school/college/University is impaired								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at All	**Slightly**		**Definitely**		**Markedly**		**Very severely impaired / Cannot work**	

Because of my IBS my home management is impaired (cleaning, shopping, cooking, child care, paying bills, etc)								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at All	**Slightly**		**Definitely**		**Markedly**		**Very severely impaired**	

Because of my IBS my social & leisure activities are impaired (activities with other people, e.g. outings, visitors, parties, etc)								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at All	**Slightly**		**Definitely**		**Markedly**		**Very severely impaired**	

Because of my IBS my private leisure activities are impaired (activities done alone, e.g. reading, gardening, walking alone, sewing, etc)								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at All	**Slightly**		**Definitely**		**Markedly**		**Very severely impaired /**	

Because of my IBS my ability to form and maintain relationships is impaired								
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Not at All	**Slightly**		**Definitely**		**Markedly**		**Very severely impaired**	

Illness Perception Questionnaire adapted for IBS (IPQ)

About Your IBS

For the following questions, please circle the number that best corresponds to your views about your IBS:

How much does your IBS affect your life?										
0	1	2	3	4	5	6	7	8	9	10
no affect at all										severely affects my life
How long do you think your IBS will continue?										
0	1	2	3	4	5	6	7	8	9	10
a very short time										forever
How much control do you feel you have over your IBS symptoms?										
0	1	2	3	4	5	6	7	8	9	10
absolutely no control										extreme amount of control
How much do you think treatment can help your IBS?										
0	1	2	3	4	5	6	7	8	9	10
not at all										extremely helpful
How much do you experience symptoms from IBS?										
0	1	2	3	4	5	6	7	8	9	10
No symptoms at all										many severe symptoms
How concerned are you about your IBS?										
0	1	2	3	4	5	6	7	8	9	10
not at all concerned										extremely concerned
How well do you feel you understand your IBS?										
0	1	2	3	4	5	6	7	8	9	10
don't understand at all										understand very clearly
How much does your IBS affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)										
0	1	2	3	4	5	6	7	8	9	10
not at all affected										extremely affected

Cognitive scale for functional bowel disorders (CS-FBD) questionnaire

About Your IBS continued

For the next questions, please indicate (tick) the response that best applies to you over the past month.

	Strongly disagree	Disagree	Slightly disagree	Neutral	Slightly agree	Agree	Strongly agree
1. I often worry that there might not be a bathroom available when I need it.	○	○	○	○	○	○	○
2. I cannot function normally when I get bowel symptoms.	○	○	○	○	○	○	○
3. I often worry about passing gas in public.	○	○	○	○	○	○	○
4. When I have bowel symptoms I'm in agony.	○	○	○	○	○	○	○
5. It's important to do my absolute best at everything I try.	○	○	○	○	○	○	○
6. I am constantly frustrated by my bowel symptoms.	○	○	○	○	○	○	○
7. I often feel that this abdominal pain will never go away.	○	○	○	○	○	○	○
8. Having bowel symptoms interferes with my feeling good about myself.	○	○	○	○	○	○	○
9. I worry that if I go on a trip I will have bowel problems.	○	○	○	○	○	○	○

Please indicate (tick) the response that best applies to you over the past month.

	Strongly disagree	Disagree	Slightly disagree	Neutral	Slightly agree	Agree	Strongly agree
10. I often worry that I won't be able to concentrate because of abdominal pain.	○	○	○	○	○	○	○
11. It is extremely embarrassing to have to keep going to the bathroom.	○	○	○	○	○	○	○
12. I am often concerned about lasting through an event because of my bowel problems.	○	○	○	○	○	○	○
13. The idea of being late upsets me.	○	○	○	○	○	○	○
14. I often feel very down about my symptoms.	○	○	○	○	○	○	○
15. I hate the thought of making a fool of myself in front of other people.	○	○	○	○	○	○	○
16. My bowel symptoms make me feel out of control.	○	○	○	○	○	○	○
17. If I go out to eat in a restaurant, I often worry that I will have bowel symptoms.	○	○	○	○	○	○	○
18. My bowel problems keep me from taking advantage of opportunities.	○	○	○	○	○	○	○
19. If I go to the bathroom frequently, other people will think that there's something wrong with me.	○	○	○	○	○	○	○

Please indicate (tick) the response that best applies to you <u>over the past month.</u>

	Strongly disagree	Disagree	Slightly disagree	Neutral	Slightly agree	Agree	Strongly agree
20. I feel that my bowel symptoms are too much for me to handle.	○	○	○	○	○	○	○
21. I constantly worry about losing control of my bowels when I'm out somewhere.	○	○	○	○	○	○	○
22. I feel guilty if I spend time nurturing myself.	○	○	○	○	○	○	○
23. I often worry about not having enough time to get to the bathroom.	○	○	○	○	○	○	○
24. When I am getting bowel symptoms, I feel like I have to get home immediately.	○	○	○	○	○	○	○
25. I feel that I am always sick with bowel problems.	○	○	○	○	○	○	○
26. Because of my bowel problems, I become anxious when I think about upcoming social events.	○	○	○	○	○	○	○
27. I often give up my own wishes in order to make other people happy.	○	○	○	○	○	○	○
28. I do things I don't want to do, just to avoid confrontation.	○	○	○	○	○	○	○
29. I frequently worry about getting stuck in traffic and not being able to get to a bathroom.	○	○	○	○	○	○	○
30. I often worry that other people will hear my stomach make noises.	○	○	○	○	○	○	○
31. Nothing seems to help my bowel symptoms.	○	○	○	○	○	○	○

Behavioural responses questionnaire (BRQ)

For the following questions, please indicate (tick) the best response that best applies to you from 1 (never) to 7 (always):

	Never 1	2	3	4	5	6	Always 7
1. I eat specific foods to help me open my bowels more.	○	○	○	○	○	○	○
2. I eat specific foods to help me open my bowels less.	○	○	○	○	○	○	○
3. I strain when opening my bowels.	○	○	○	○	○	○	○
4. After opening my bowels I check for blood.	○	○	○	○	○	○	○
5. After opening my bowels I check my stool for abnormalities.	○	○	○	○	○	○	○
6. I spend more time on the toilet than I ideally would like.	○	○	○	○	○	○	○
7. I often go to the toilet to open my bowels and then do not pass anything.	○	○	○	○	○	○	○
8. I often go to the toilet to pass water and find I open my bowels.	○	○	○	○	○	○	○
9. I avoid exercise when I have stomach pains.	○	○	○	○	○	○	○
10. I avoid certain foods when I have bowel problems.	○	○	○	○	○	○	○

Please indicate (tick) the best response that best applies to you from 1 (never) to 7 (always):

	Never						Always
	1	2	3	4	5	6	7
11. I wear baggy clothing when my stomach feels bloated or distended.	○	○	○	○	○	○	○
12. I avoid going out in case I have problems with my IBS.	○	○	○	○	○	○	○
13. I avoid making plans in case I have problems with my IBS.	○	○	○	○	○	○	○
14. I carry other items (e.g. wet wipes, sanitary towels, spare underwear) in case my IBS flares up.	○	○	○	○	○	○	○
15. I take medication (e.g. before going out) just in case my IBS flares up.	○	○	○	○	○	○	○
16. I carry medication with me in case my IBS flares up.	○	○	○	○	○	○	○
17. I avoid sex in case my IBS flares up (and causes embarrassment).	○	○	○	○	○	○	○
18. When I go out I make sure I know where the nearest toilet is.	○	○	○	○	○	○	○

Please indicate (tick) the best response that best applies to you from 1 (never) to 7 (always):

	Never 1	2	3	4	5	6	Always 7
19. I ask for reassurance about my IBS.	○	○	○	○	○	○	○
20. I avoid certain work situations (e.g. meetings) because of my IBS.	○	○	○	○	○	○	○
21. I avoid certain social situations (e.g. restaurants) because of my IBS.	○	○	○	○	○	○	○
22. I avoid certain foods (e.g. dairy products, spicy foods) because of my IBS.	○	○	○	○	○	○	○
23. After I open my bowels I wipe more than I would like.	○	○	○	○	○	○	○
24. When I have diarrhoea I do things to ease it (e.g. take prescribed medication, take alternative medication).	○	○	○	○	○	○	○
25. I am constantly aware of my stomach.	○	○	○	○	○	○	○
26. I avoid staying away from home overnight in case my IBS flares up.	○	○	○	○	○	○	○

Hospital anxiety and depression scale (HADS)

About how you feel

For the following questions, please indicate (tick) the response that best applies to how you have felt in the past week:

1. I feel tense or 'wound up'

Most of the time	A lot of the time	From time to time, occasionally	Not at all

2. I still enjoy the things I used to enjoy.

Definitely as much	Not quite so much	Only a little	Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen.

Very definitely and quite badly	Yes, but not too badly	A little, but it doesn't worry me	Not at all

4. I can laugh and see the funny side of things.

As much as I always could	Not quite so much now	Definitely not so much now	Not at all

5. Worrying thoughts go through my mind.

A great deal of the time	A lot of the time	Not too often	Very little

6. I feel cheerful.

Never	Not often	Sometimes	Most of the time

7. I can sit at ease and feel relaxed.

Definitely	Usually	Not often	Not at all

Please indicate (tick) the response that best applies to how you have felt <u>in the past week:</u>

8. I feel as if I am slowed down

○ Nearly all the time	○ Very often	○ Sometimes	○ Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach.

○ Not at all	○ Occasionally	○ Quite often	○ Very often

10. I have lost interest in my appearance.

○ Definitely	○ I don't take as much care as I should	○ I may not take quite as much care	○ I take just as much care as ever

11. I feel restless as if I have to be on the move.

○ Very much indeed	○ Quite a lot	○ Not very much	○ Not at all

12. I look forward with enjoyment to things.

○ As much as I ever did	○ Rather less than I used to	○ Definitely less than I used to	○ Hardly at all

13. I get sudden feelings of panic.

○ Very often indeed	○ Quite often	○ Not very often	○ Not at all

14. I can enjoy a good book or radio or television programme.

○ Often	○ Sometimes	○ Not often	○ Very seldom

Appendix E

NICE Guidelines

Irritable bowel syndrome and diet

NHS National Institute for Health and Clinical Excellence

What is irritable bowel syndrome (IBS)?

IBS is a very common condition. It describes a wide range of symptoms that vary from one person to another and can be worse for some people than others.

The most common symptoms are:

- wind and/or bloating
- diarrhoea or constipation, or both
- low abdominal pain, which may ease after opening the bowels or be accompanied by a change in bowel habit or stool appearance
- passing mucus
- feeling the need to open the bowels even after having just been to the toilet
- a feeling of urgency
- feeling that your symptoms are worse after eating.

If you have any of the following symptoms consult your doctor immediately:

unintentional and unexplained weight loss; rectal bleeding; a family history of bowel or ovarian cancer; if you are over 60 years old, a change in bowel habit to looser and/or more frequent stools for more than 6 weeks. Before attempting to manage symptoms via your diet, it is important to rule our other medical conditions, and to have a diagnosis established by your doctor or healthcare professional.

Ensure that you:

- eat regular meals
- do not skip meals or eat late at night
- take your time when eating meals
- sit down to eat and chew your food well
- take regular exercise – for example, walking, cycling or swimming
- make time to relax.

Helpful hints:

- keep a food and symptom diary to see if diet affects your symptoms. Remember symptoms may not be caused by the food you have just eaten, but what you ate earlier that day or the day before.
- give your bowels time to adjust to any changes that you make.

Make changes according to your current symptoms

For symptoms of wind and bloating

- Limit fruit to 3 portions a day (including up to 1 portion of dried fruit if wanted) and fruit juice to 1 small glass a day. Remember to make up the recommended '5 a day' with vegetables.
- Try reducing your intake of resistant starches (see box below).
- Oats and golden linseeds may also help with symptoms of wind and bloating.
- If you wish to try 'probiotics' the information under 'symptoms of diarrhoea' overleaf may be useful.

How much is 1 portion of fruit or vegetables?

Fresh fruit = 80 g

- 1 apple, banana, pear, orange or similar sized fruit,
- ½ grapefruit, 1 slice of large fruit (melon, pineapple)
- 2 plums
- a handful of grapes, cherries, berries
- 3 heaped tablespoons fruit salad (fresh, tinned, stewed)

Dried fruit = 25 g

- 1 heaped tablespoon raisins, figs, apricots

Vegetables = 80 g

- 3 heaped tablespoons raw, cooked, frozen or tinned vegetables
- a dessert bowl of salad

Resistant starches

- These are the starches in foods that are not completely digested by the body. They enter the bowel where they ferment and produce gas. Try reducing your intake of the following foods:
- pulses, whole grains, sweetcorn, green bananas and muesli that contains bran
- undercooked or reheated potato or maize/corn – instead eat them freshly cooked and still hot
- oven chips, crisps, potato waffles, fried rice – choose baked potatoes or boiled rice
- part-baked and reheated breads, such as garlic bread, pizza base – choose fresh breads
- processed food such as potato or pasta salad, or manufactured biscuits and cakes
- ready meals containing pasta or potato, such as lasagne, shepherd's pie, macaroni cheese
- dried pasta – use fresh pasta instead.

Appendix F

Therapy protocols and structures

Kennedy et al (2005)

Appendix 2

Irritable bowel syndrome specific cognitive behavioural therapy: a manual for primary care

Introduction

This manual outlines the psychological treatment approach developed as part of a large randomised controlled trial of cognitive behavioural psychotherapy and antispasmodic therapy versus antispasmodic therapy alone for irritable bowel syndrome. General nurses in primary care were trained to deliver the cognitive behavioural therapy.

Irritable bowel syndrome (IBS)

Irritable bowel syndrome is the most common functional disorder and depending on the criteria used to make a diagnosis affects approximately 15–20% of the general UK population. The condition is non-life-threatening and is twice as common in women as in men.

IBS is characterised by the presence of abdominal pain and altered bowel habit with characteristic symptoms summarised in the box below. These symptoms, known as the Manning criteria, aid the diagnosis of IBS and the more of the symptoms that are present the more likely that the diagnosis is IBS. Other researchers have refined the diagnosis of IBS and although there is no diagnostic test for IBS there are a few factors that aid diagnosis.

In primary care most patients who consult regarding symptoms of IBS are in their late twenties or early thirties and will often have had symptoms for several years prior to consulting. Weight loss, nocturnal pain and gastrointestinal blood loss are not features of IBS and should alert one to the possibility of more serious pathology. One should consider referral for further investigation including lower gastrointestinal endoscopy if patients present with new gastrointestinal symptoms or a change in pre-existing ones after the age of 45 years. Patients at a younger age should be referred if there is a history of colorectal cancer in a first degree relative. At any age one should consider the possibility of inflammatory bowel disease (IBD), a more dangerous condition than IBS and one that may share its symptom profile. Performing a full blood count and a C-reactive protein (CRP) or erythrocyte sedimentation rate (three blood tests) helps in the detection of IBD and anaemia and abnormal results should prompt referral. There is uncertainty regarding the need to screen for coeliac disease, a condition characterised by an intolerance of gliadin, a protein found in wheat and certain other grains. The availability of a serological screening test does facilitate testing if this is considered appropriate.

The symptoms of IBS can be distressing, inconvenient and often disruptive. Although it seems the majority of patients with IBS do not consult about it, for some patients the condition is troubling and reduces their quality of life and their productivity. It is a remitting relapsing condition and there is no cure. The one-time association between IBS and psychiatric disorder is now considered to be due to consultation and referral bias. Although patients with IBS who are referred to secondary care do report a considerable degree of psychopathology this is tempered by the finding that patients with IBS in the general population who do not consult have normal psychological profiles. It is now thought that the reported gradation in psychopathology from non-consulters to consulters is a feature of consulting behaviour rather than of IBS. Similar findings have been shown for other medically unexplained conditions such as non-cardiac chest pain and chronic fatigue syndrome. Those patients with IBS who do consult report greater

Manning criteria to aid diagnosis of IBS
Recurrent abdominal pain and two or more of the following:

- Relief of pain with defecation
- More frequent stools at the onset of pain
- Looser stools at the onset of pain
- Visible abdominal distension
- Passage of mucus per rectum
- Sensation of incomplete evacuation

IBS is identified in patients with recurrent abdominal pain and two or more of the Meaning criteria.

severity of abdominal pain than do non-consulters and they also report a fear that their symptoms may be due to more serious conditions such as gastrointestinal cancer or heart disease.

Many patients report that their symptoms are worse when they are stressed, but as the pathophysiology of IBS is imperfectly understood it is uncertain as to how this is mediated. A commonly held theory is that IBS may be at least partly due to hypersensitivity of the enteric nervous system; that is the plexi of nerves that line the bowel may be overly sensitive and may respond to a level of stimulus that would not normally produce a response. The gut may then also be over-responsive and demonstrate excessive or aberrant motility.

Understanding where cognitive behavioural therapy (CBT) fits in

Key point: CBT is not a cure for IBS.

CBT is not a panacea and it is to be expected that patients with IBS will continue to experience symptoms after completing their CBT. Neither is CBT as presented here in conflict with therapy the patient may already be taking. We would expect patients to experience symptoms associated with irritable bowel syndrome after the treatment has been completed. CBT focuses on the behaviours, thoughts and feelings surrounding IBS. The aim is to improve the way people cope with day-to-day life. By improving these aspects it is hoped that the patient's perception of the physical symptoms of IBS will also improve.

The cognitive behavioural treatment rationale: the three systems model

Key point: Thoughts, behaviour and feelings maintain and intensify symptoms.

The way a patient thinks, acts and feels can intensify and maintain the symptoms of IBS. When a patient experiences pain, bloating, constipation or diarrhoea the way he/she then thinks about the symptoms will affect their levels of anxiety.

For example a patient may think, 'oh no. I've got that pain again. I've had it for a while now, that must mean that there is more to this than just IBS, the doctor must be wrong. I have something more serious'. Such thoughts may increase levels of anxiety and result in a perception of more severe symptoms culminating in associated behaviours such as an increase in consultation with a general practitioner and a request for referral to a specialist. We know for example that patients who continue to attribute their symptoms to a purely physical cause are more likely to consult than those who do not. The patient may then go on to develop other behaviours such as altering diet, symptom monitoring, straining and avoiding social situations in an attempt to gain control over and reduce the symptoms or to avoid the consequences of the symptoms that may result from embarrassment. Patients may become trapped in a vicious circle of fear and avoidance; these three systems, the physiological, cognitive and behavioural responses, appear to be interdependent and responsible for maintaining the disorder. Changing cognitions, behaviour or both is likely to bring about improvement in symptoms.

We can see how a person's thoughts, feelings and behaviours will affect how they respond to the symptoms. This in turn will affect many aspects of their daily life.

If patients experience a particularly nasty bout of symptoms they might focus on the symptoms much more (becoming hypersensitive to them) which in turn may then increase the impact and frequency of the IBS symptoms. This is referred to as symptom focusing.

The patient should understand that this does not mean that IBS is all in the mind. Rather, even though IBS may have physical causes that we do not fully understand, a CBT approach assumes

Case example

Kate has an important meeting with her boss in the morning that causes her some anxiety (feelings and thoughts).

She knows that these sorts of situations often cause her IBS to flare up, and cause more diarrhoea and bloating than usual.

She is further concerned that her diarrhoea will cause her to leave the meeting early (thought).

She decides to call in sick from work with diarrhoea (behaviour).

She then feels guilty and depressed about the effect of her IBS on her life (feelings and thoughts).

Kate thinks that maybe she should give up her job if she can't manage to go to meetings (behaviour and thoughts).

that what a person does, thinks and feels will aggravate and maintain many of the IBS symptoms. A CBT approach assumes that IBS is likely to be influenced by and to influence a patient's lifestyle, level of anxiety and the way he/she views the world. Therefore if possible during the assessment ascertain which thoughts and behaviours are aggravating or maintaining IBS symptoms.

The cognitive behavioural treatment rationale: engagement

Key point: Fit the CBT model to the patient's own experience of IBS.

Once the patient can understand the CBT model and how it fits with their own experience of IBS then the therapist should explain how further sessions will aim to lessen the impact of IBS and in turn reduce the symptoms.

The therapist should explain to the patient that treatment is collaborative, i.e. the therapist and patient will work together to identify possible maintaining factors. They can then test out different ways of coping with IBS. This style of therapy is often referred to as 'collaborative empiricism'. Thoughts and behaviours that may be maintaining aspects of the IBS are identified and alternative behaviours are suggested and tested.

The therapist should demonstrate a positive regard for the patient and their problems. The therapist should try to avoid using medical jargon and where possible use the patient's language. The therapist needs to have a good working knowledge of IBS and the problems associated with it.

Case example
Jane and her therapist identified the following possible maintaining behaviour. Jane avoided walking with her boyfriend for fear of being caught short without a public toilet and being incontinent. She had never been incontinent in the past. This restricted her life and affected her relationship with her boyfriend. She agreed to test out her fear and risk walking with her boyfriend without knowing where the toilet was. She subsequently found that even though she did have some urge to go to the toilet, she was able to control this until reaching a convenient place. By the end of treatment she was able to go into any situation without knowledge of where toilets were located and no longer avoided walking with her boyfriend.

Treatment does not focus on cause and onset. The patient is likely to still have IBS at the end of treatment and they will still have bouts of symptoms. The aim of treatment is to help the patient manage these symptoms in a way that will have minimal effect on their individual lifestyle.

Treatment outline

Each patient is offered six sessions of CBT lasting 50 minutes each. The following is an outline of the content of each session and the techniques that one might use.

All sessions should include

1. consent for tape recording the session in order to facilitate review with a CBT tutor
2. collaborative agenda setting.

Session 1 will focus on a cognitive behavioural assessment and defining problems and goals of treatment.

Sessions 2–6 will include the following:
1. feedback from previous session
2. homework review
3. homework discussion
4. goal setting
5. recap of key issues.

The treatment sessions will also include the following components as necessary:

1. information giving about the problems associated with IBS
2. continuing to identify maintaining factors in IBS
3. introducing IBS specific behavioural and cognitive strategies
4. checking understanding and acceptance of the treatment rationale
5. using questionnaires as a therapeutic tool to monitor progress
6. encouraging the use of diaries.

Specific session by session outline

Session 1

Assessment, engagement and problems and targets

Aims:

1. to build a therapeutic relationship
2. to obtain a detailed problem analysis

3. to agree a specific problem statement
4. to agree on a minimum of two specific treatment goals
5. to ensure the rationale of treatment is understood and agreed and the patient is willing to engage for six sessions using this approach.

A CBT assessment for IBS will involve the therapist gathering details about the patient's IBS, including reviewing the patient's symptoms in detail, explaining how the therapy may be able to help and agreeing on goals that the patient would like to achieve by the end of treatment.

The CBT assessment broadly focuses on five areas based on the identification of; the main problem associated with IBS, maintaining behaviours, maintaining cognitions, precipitating factors and discussion of the impact of IBS on the patient's life.

Main symptom identification
Useful questions in this area include: Can you tell me about your main symptoms in your own words? How does your IBS affect you physically? The following areas are enquired about: pain, diarrhoea, constipation, changing bowel pattern, tenesmus (non-productive straining at stool), bloating, mucus and flatulence.

Other useful questions in this area include: What about problems during the day/night? How long does it last? What do you usually do when you get the pain? Is there anything that makes it better/worse? Do any particular foods make it better/worse? How does stress/anxiety affect your symptoms? Does IBS affect your sex life? Does IBS affect your menstrual cycle? What else triggers the symptoms?

Identifying maintaining behaviours
Useful questions in this area include: How does IBS affect what you do? Is there anything you avoid because of the problem? Do you avoid certain places or particular food? Is there anything you currently do more than you ideally would like to, for example spending too much time on the toilet or needing to be aware of where the nearest toilet is? Are there particular things that you do when you go to the toilet that trouble you, for example straining, excessive wiping, checking for abnormalities? How many times do you go to the toilet and not pass anything?

Identifying maintaining cognitions
Useful questions in this area include: What thoughts/images do you have about IBS? What specific worries do you have with regard to IBS? What do you believe is the worst thing that could happen to you because of IBS? Determine how strongly the belief is held and determine whether the belief makes the patient feel emotionally anxious, angry, frustrated or low.

Identifying precipitating factors
Useful questions in this area include: When did this problem start? What was happening at that time? Was there a specific incident? Did you get stomach ache as a child? How did your family react? Did anyone in your close family have similar symptoms? Do they now? Is there any pattern to when your IBS is worse? Is there any pattern to when it is better?

Detailing the impact of IBS on a patient's life
Useful questions include: What impact does IBS have on your life or on the lives of others around you? Why have you come for treatment now?

An example of the rationale
Pain or discomfort in the abdomen, diarrhoea, flatulence and constipation occurs to most of us at some stage.

If you experience a particularly nasty bout of symptoms this can make you vulnerable to experiencing these symptoms more and more.

IBS is not a typical physical disease, it is a problem affecting the way the digestive system functions.

It cannot kill you and is unlikely to get much worse.

It normally comes and goes.

For some people IBS will go away completely and for others it will never totally get better.

Once you can accept the natural progress of IBS you can learn to control it.

This will make it much easier to live with and may even stop it for good.

It is thought that IBS is aggravated by stress.

This does not mean that IBS is all in the mind; far from it, IBS may have physical causes, but what you do, think and feel aggravates and maintains many of these physical causes.

IBS is likely to be connected to your lifestyle, to your level of anxiety and to the way you view the world and your IBS symptoms.

By looking at and modifying what you feel, think and do you will reduce the impact of IBS and lead a less restricted life.

It is OK to have IBS. It is nothing to be ashamed or apologetic about.

There are lots of things you can do to reduce the effect it has on you.

Explaining the treatment rationale

Once a clear understanding of the above areas is obtained the therapist will be able to explain the treatment rationale to the patient using examples from the patient's own history. Any explanation should be jargon free. Time should be spent making sure that the patient fully understands the rationale as this is an essential component of the therapy.

Once the rationale has been understood the goals of therapy should be reviewed. These are used as a basis from which to agree end of treatment targets which the patient and therapist rate at the beginning, middle and end of treatment. These targets are rated on a 0–8 scale, 0 indicating the patient is able to reach this target now without difficulty and 8 indicating that the target is unachievable at present. Define and rate a minimum of two long-term targets. Sample pieces of behaviour can be taken from different areas of the patient's life. This may be work, social, home management or personal.

It is important that these target statements contain specific, realistic and measurable samples of coping behaviour that the patient wishes to alter.

Example: end of treatment targets

- To use the gym for 1 hour 3 times weekly
- To be able to attend unplanned meetings for their duration without going to the toilet beforehand
- To use the toilet only when I have an urge to
- To eat three meals a day at regular intervals

Sometimes it is difficult to agree on long-term problems and targets in the first session. The therapist may suggest that the patient make a list of the goals of therapy before the next session.

First week's goal

From the long-term targets, an initial first goal may be agreed with the patient. This should be a small specific behaviour that the patient can identify as being a positive step in improving behaviour associated with their IBS, e.g. to spend a maximum of 15 minutes on the toilet each time I go this week.

This goal should have an approximately 85% chance of being successfully achieved within the following week. Therapist and patient will check for any possible problems or obstacles that may arise in the completion of this goal and will deal with these or adjust the goal accordingly.

Monitoring symptoms and behaviour

The patients are asked to use a diary for one week only in which to monitor symptom severity and the situations in which symptoms occur. Patients are asked to record the situations in which the symptoms arise and their thoughts and behaviours associated with these symptoms.

The aim of this diary is to gather information about the day-to-day effects of symptoms and behaviour and to provide information on which to construct targets during future therapy sessions.

Therapists should warn patients that focusing on symptoms for the first week may cause the symptoms to get worse. This may be used as an example of how focusing causes symptoms to increase.

Session 2

After an agenda has been agreed, the patient feeds back on the initial session.

If an initial target was set at session 1, this should be reviewed and problems associated with it discussed. Agreement should be reached as to the value of this target, how it relates to the CBT model and how it may be developed further.

The symptom-monitoring diary completed during the previous week is reviewed, looking for themes and trends in behaviour and cognitions.

A common example is that the patient fears that symptoms of IBS may mean they have cancer or a more serious illness. They may check their stools for blood or 'abnormalities'. They may worry that if they do not produce the 'ideal stool' then something must be seriously wrong.

Another patient may fear that the symptoms are uncontrollable and may worry about passing wind in public and the resulting embarrassment.

The therapist and patient will then identify, prioritise and agree upon targets for the following week. If possible these should be behavioural targets either facing previously avoided behaviour or reducing excess precautions or safety behaviour.

Example of second week's targets

- Not to read every time I use the toilet
- To use the toilet only when I have a definite urge to pass a stool
- To visit the cinema once a week (or another activity) without using the toilet for 1 hour before
- To eat two slices of toast for breakfast every weekday
- Not to check my stool for abnormalities this week
- Not to carry my IBS medication when going outside this week

The specific weekly targets chosen will vary according to each individual's needs and circumstances. The patient is encouraged to take a lead in choosing target behaviours from the first week's diary. His/her commitment is sought to undertake these targets even when symptomatic and not to abandon them when symptoms develop but to continue to practise according to an agreed, preset timetable. Patients are encouraged to telephone their therapist if they have any difficulties in between sessions. Homework diaries are given, with an explanation of how to complete them. Homework diaries record the particular targets and the patient's success on reaching these with records of each event associated with the target.

Session 3

The patient's reactions to the previous session, and homework are explored.

The homework and self-monitoring diaries are reviewed, new homework targets are set and any setbacks or difficulties are problem solved.

Sessions 3–6 are conducted in a similar manner, reinforcing the links between thoughts, feelings and behaviour, with specific strategies for specific symptoms.

These sessions involve:

1. reviewing the homework and self-monitoring diaries
2. eliciting the patient's reaction
3. rechecking the patient's acceptance and understanding of the treatment model
4. identifying specific difficulties in achieving the patient's targets
5. adopting a collaborative, problem-solving approach to any difficulties
6. setting new targets
7. predicting problems and generating potential solutions
8. emphasising the importance of maintaining a consistent programme.

Sessions 4 and 5

These sessions will also include education and discussion about how to challenge negative thoughts. An example of a negative thought would be regularity is next to godliness – if you empty your bowels regularly then you're in good health. My bowels are not regular so I must be unhealthy.

The negative thought diaries are reviewed and contents are discussed. The therapist will highlight the link between thoughts and symptoms and how negative thoughts increase the severity and frequency of symptoms. Illness attributions, self-esteem, performance and expectations will also be examined. If the patient has had difficulty identifying negative thoughts, this should be explored in more detail.

Methods of evaluating and looking at alternative thoughts are discussed: the therapist and patient can discuss the evidence for and against the negative thought, they can consider an alternative view, examine the advantages and disadvantages of a negative thinking style and look at logical thinking errors.

It is important that alternative thoughts are elicited from patients in a collaborative manner so that they learn to re-evaluate their thinking themselves. Instruction is given on the use of dysfunctional thought diaries, including recording alternative more helpful thoughts.

Session 6

This session will also include preparation for discharge and relapse prevention techniques. From session 4 there will have been an increasing delegation of responsibility for therapy. The patient is now expected to continue the behavioural and cognitive skills they have learned without requiring prompting from the therapist.

The aims of this final session are:

1. to anticipate setbacks and write a relapse plan preparing the patient for potential difficulties and setbacks in the future
2. to ensure that progress continues after active treatment is completed
3. to develop the patient's confidence and ability to deal appropriately with setbacks without relapsing. The patient is advised that this ability will wax and wane
4. to ensure that the patient's lifestyle and long-term plans are realistic and will facilitate the maintenance of therapy gains.

The idea that symptoms will continue to arise from time to time should be reinforced, as should the concept that the patient will be able to deal with them effectively. Patients are encouraged to write a list of what they have learnt/found most useful in treatment and to plan mini-programmes to deal with potential setbacks. This 'cue card' can be used as a reminder and prompt when problems arise in the future.

The patient and therapist should anticipate future problems and develop appropriate coping strategies. These can also be highlighted on the cue card. Session 6 should occur no longer than 9 weeks after the start of treatment. After this time all patients will be reassessed for improvements.

The kitbag approach

As specific issues arise the therapist will identify the specific technique that may be appropriate from a 'therapeutic kitbag'. The kitbag is a collection of techniques that have been derived from the cognitive behavioural model to address specific issues that often arise with patients with IBS. These will be used throughout treatment. The identification of the appropriate technique and the specific technique to use will rely on good communication between patient and therapist.

The kitbag can be divided into five sections.

1. Educational advice

Education and advice may be given to inform any misconceptions concerning bowel function.

Some of the common misconceptions are listed below:

Frequency and consistency of stool motion

Examples of misconceptions
'I should pass a stool every day'
'Stools must be a certain shape and form'

The hunt for the perfect stool: some patients will examine each stool that they pass, wanting to achieve a perfect stool that will never be achieved.

Therapists may discuss what affects the frequency and consistency of stools, the role of diet, stress, anxiety and worry or change of environment.

The nature of the digestive system

Example of misconceptions
'It is dirty/dangerous to be unable to get rid of all of my stool'

Therapists should have a working knowledge of the digestive system and how food passes through the body. For example, patients can be informed that the bowel is never completely empty.

The role of diet

Example of misconceptions
'By avoiding certain food I will avoid/control my symptoms'

'By avoiding eating at certain times I will avoid/control certain symptoms'

Some misconceptions will also contain statements that need a more cognitive intervention, e.g. 'should' statements. This approach is outlined below.

Misinterpretation of IBS symptoms

Some of the symptoms of IBS are often misinterpreted.

Example of symptom misinterpretation
Tricia often experiences a feeling of incomplete evacuation (a very common symptom in IBS). When experiencing this symptom she believes she must pass a stool because if she does not she believes she will suffer harm or damage. This leads to excessive straining or even occasional manual evacuation in the attempt to reduce this feeling.

During the session these thoughts and their resulting behaviour were discussed. It was explained that the feeling of incomplete evacuation is a symptom of IBS and does not mean that the Tricia must pass a stool. Once Tricia understood this, she was advised just to experience the symptom and not to react in the previous manner.

She was able to learn to distinguish between this feeling of incomplete evacuation and the actual feeling that she needed to pass a stool.

2. Behavioural techniques

Reintroducing avoided foods

Rationale: Often people with IBS may link specific foods and drinks to their symptoms. These are often very idiosyncratic and associations are frequently made after only one bad experience, e.g. I got the runs after drinking Ribena, and so I avoid it totally now. This can cause moderate to severe limitations on a person's life. Whilst in treatment it is an ideal opportunity to re-test these associations in a systematic way. The therapist can explain to patients that after re-testing previously avoided foods in a systematic manner they will be in a better position to make a decision about their exclusion of these from their diet.

Technique:

- Ask patients to make a list of avoided foods.
- Ask them to decide which food would be a good starting point to try and face. These may be foods that they would like/should be able to

eat/they think are good for them to eat. It may be that the avoidance of these foods is causing disruption to the patient's life.
- Agree and set targets for foods to try in the following 2 weeks specifying the frequency and amount of food to be eaten.
- Predict and prepare solutions for problems that may occur.

Improving toileting behaviour

Rationale: The act of going to the toilet often involves many microbehaviours that may help maintain IBS symptoms. As with food avoidance these behaviours need to be assessed and reduced.

Examples of microtoileting behaviour
- Excessive wiping, checking or time spent on toilet
- Manual evacuation

Straining: this is probably the most important behaviour to assess and reduce. Patients often strain because they feel they will be unable to pass a stool without doing so. Patients may strain for long periods of time and still only manage to pass small stools if any at all. The patient and therapist assess the length of time spent straining and the severity of the 'push' and agree on how this will be reduced. The aim should be to have completely stopped straining by the end of treatment.

3. Cognitive techniques

The role of negative automatic thoughts in maintaining IBS is discussed, the relationship of these thoughts to feelings and behaviour is explored, and there may be misconceptions about bowel habit. It is emphasised that negative automatic thoughts can initially be hard to identify. They are explained as distortions of reality that can influence the perception, response to and maintenance of symptoms, and that can lower mood.

Self-monitoring diaries

Self-monitoring diaries for thoughts are introduced, and their use is explained, reinforcing the feeling/thoughts/behaviour link. Patients are asked to record examples of situations in which they experience an unpleasant emotion or mood change, and to write down as exactly as possible what is going through their mind at the time.

Patients should be prepared for the possibility that recording negative thoughts may, by heightening awareness, temporarily increase feelings of depression or an increase in symptom sensitivity. Patients should be advised, if this occurs, to limit the time spent focusing on distressing thoughts.

Once these diaries have been completed the therapist and patient will use them to identify common themes and thinking errors and then to discuss suitable alternatives that may be used.

Testing out predictions

Examples of predictions patients make
- 'Others will notice the smell'
- 'I will have an accident if I wait more than one minute'

There are many ways to challenge thoughts. Therapists should use the ways they feel appropriate for the patient and situation. A number of ways that we have found helpful to challenge people's thoughts are suggested below.

The cake technique

Example of cognitive misconception
- 'My doctor has missed something that will cause me irrevocable harm'

The cake technique asks patients to list all possible alternatives and then to allocate percentage chances of each occurring as part of a cake (made up of 100%). As more and more possible alternatives are suggested and allocated a 'piece of the cake' the total percentage will usually be over 100% (sometimes many times more). This is a visual technique that allows patients to see how easy it is to overestimate the chances of a serious illness or that the GP has made a mistake.

The for and against technique

Example of belief
'I have a serious illness like bowel cancer'

Once the belief is identified, patients are asked to list statements that support the statement. They are then asked to rate their strength of belief for each statement. Next they list statements that disprove the belief, as well as rating the strength of belief in each. They are then asked to reassess their original statements.

4. Symptom management techniques

Reducing symptom focusing

Rationale: Bloating and abdominal pain are common symptoms of IBS. By attending to the abdominal area people are more likely to have an

increased sensitivity to any abdominal change. Once you focus on abdominal symptoms one is likely to experience more abdominal pain and bloating and to notice them with increasing frequency. By using a range of techniques we can reduce symptom focusing and thus reduce pain and bloating.

Techniques: Patients are asked to watch out for when they make predictions about the onset of bloating and pain.

Example of symptom focusing
'I have just eaten a cheese roll, that's going to give me hell!'

The therapist may respond by explaining:
'Once we have these types of thoughts we are more likely to focus on the abdominal area. This will make us more sensitive to any changes that may have occurred anyway. Once we have felt a change we are more likely to think in ways that support our previous assertion, for example: "Oh no, I can feel it starting, its getting worse, I can't control this". These thoughts increase our focusing on the area and are more likely to exacerbate our perceptions of the severity of the symptoms.'

Patients need to be aware that when they are focusing, they must not ignore the pain, but carry on with it. The therapist will teach them to be aware of their thoughts the moment they first become aware of the symptoms and to address any unhelpful thoughts.

The getting a second head technique

When patients experience lots of negative thoughts about their symptoms, e.g. 'I'm not coping with it at all', it can be helpful to put a distance between themselves and the thought. This is what the second head technique is designed to do. It allows the patient to identify negative thoughts and makes it easier for them to come up with alternatives.

Explain to patients that when they get these negative thoughts they can imagine themselves stepping out of their head and looking at their thoughts and symptoms from another perspective. Explain that it is the difference between 'I am not coping with it all' and 'I am having thoughts about not coping with my IBS'.

The first approach, 'I am not coping with it all', will naturally make a person feel worse. It does not allow one to do anything about the way that they feel. It is a dead-end statement.

The second approach, 'I am having thoughts about not coping with my IBS', allows one room to manoeuvre and to challenge the negative thoughts.

See your thoughts, don't **be** your thoughts.

Accepting IBS

Accepting IBS is a key stage in the reduction of symptoms. Once a patient can accept that they have IBS and not anything more serious and that they are likely to have this for some time then they will experience a reduction in anxiety and therefore fewer symptoms. Learning to accept IBS is an ongoing process and therapists and patients need to be aware that the process will continue long after therapy.

Example of what a therapist may say about accepting IBS
This sounds easy to say but it is very important in the reduction of symptoms. What do you say to yourself when you get symptoms of IBS? If you think 'Oh my god, I've started to feel bloated, it's bound to get worse and then ruin my night out' this is more likely to lead to increased worry, stress and focusing on the bloating. The way we think about our IBS will affect our symptoms. Recognise when this is happening and challenge those thoughts, for example 'OK, I have bloating, but I have had it this bad before, I will still go out and make the most of my night out. I will not let the IBS rule me. By still going out I will be in control'.

5. Mixed techniques

Special diets and food intake

Special diets have been shown to be of little benefit in IBS. It was thought, for example, that a high-fibre diet was beneficial, but recent studies have shown that this is not necessarily so. It is important that the patient does not become too obsessed with diet, otherwise their eating habits can be governed by fear that the discomfort or pain may return.

It is important to stabilise the patient's diet during treatment. This will allow the therapist and the patient to evaluate any changes made as a result of the therapy and not anything else. A constant regular diet may also help reduce some of the IBS symptoms.

Healthy bowel routine

The following is a list of basic guidelines to facilitate a healthy bowel routine

1. Keep regular mealtimes.
2. Drink sufficient liquid each day.

3. Maintain a regular programme of physical exercise and activity. We suggest three sessions a week each lasting a minimum of 30 minutes.
4. Avoid delaying the urge to have a bowel movement.
5. Avoid straining.

Specific stress management techniques

The main aim of these is to reduce autonomic activity.

Stress is caused by an imbalance in daily demands and a person's perceived coping abilities. Patients experience stress when they feel unable to cope with the demands made of them at work or at home. This is considered to be a two-way process. If a patient's perceived coping abilities outweigh the demands placed on them (for example a graduate who takes a job that does not allow them to use their expertise) then they will also experience stress.

There are a number of effective strategies that may help reduce stress levels:

1. saying 'no' to requests that will result in excessive demands
2. prioritising
3. timekeeping
4. looking after yourself, for example by taking breaks
5. asking for help/further training
6. giving yourself regular treats
7. not being hard on yourself.

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Appendix G

Post hoc power calculations for studies three and four

Outcome Variable	Pooled Standard Deviation	Effect Size	Achieved Power
Study three			
Symptom severity	92.65	.13	.42
Work and social adjustment	7.89	0	.05
Anxiety	4.01	.08	.18
Depression	3.47	0	.05
GI related cognitions	29.02	.13	.43
GI related avoidance behaviours	17.42	.29	.98*
GI related safety behaviours	10.23	.32	.99*
Study four			
Symptom severity	28.40	.08	.35
Work and social adjustment	8.54	.05	.16
Anxiety	4.07	.06	.19
Depression	3.66	.07	.31
GI related cognitions	33.39	.12	.67
GI related avoidance behaviours	18.02	.19	.98*
GI related control behaviours	10.63	.19	.99*

*denotes sufficient power achieved to detect effect where power ≥ 0.80. Effect size computed based on mean of each group, pooled standard deviation and number of participants included in each group.

Appendix H

ACTIB study protocol

Open Access Protocol

BMJ Open

Assessing Cognitive behavioural Therapy in Irritable Bowel (ACTIB): protocol for a randomised controlled trial of clinical-effectiveness and cost-effectiveness of therapist delivered cognitive behavioural therapy and web-based self-management in irritable bowel syndrome in adults

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ABSTRACT

Introduction: Irritable bowel syndrome (IBS) affects 10–22% of the UK population, with England's annual National Health Service (NHS) costs amounting to more than £200 million. Abdominal pain, bloating and altered bowel habit affect quality of life, social functioning and time off work. Current treatment relies on a positive diagnosis, reassurance, lifestyle advice and drug therapies, but many people suffer ongoing symptoms. Cognitive behaviour therapy (CBT) and self-management can be helpful, but availability is limited.

Methods and analysis: To determine the clinical- and cost-effectiveness of therapist delivered cognitive behavioural therapy (TCBT) and web-based CBT self-management (WBCBT) in IBS, 495 participants with refractory IBS will be randomised to TCBT plus treatment as usual (TAU); WBCBT plus TAU; or TAU alone. The two CBT programmes have similar content. However, TCBT consists of six, 60 min telephone CBT sessions with a therapist over 9 weeks, at home, and two 'booster' 1 hour follow-up phone calls at 4 and 8 months (8 h therapist contact time). WBCBT consists of access to a previously developed and piloted WBCBT management programme (Regul8) and three 30 min therapist telephone sessions over 9 weeks, at home, and two 'booster' 30 min follow-up phone calls at 4 and 8 months (2½ h therapist contact time). Clinical effectiveness will be assessed by examining the difference between arms in the IBS Symptom Severity Score (IBS SSS) and Work and Social Adjustment Scale (WASAS) at 12 months from randomisation. Cost-effectiveness will combine measures of resource use with the IBS SSS at 12 months and quality-adjusted life years.

Ethics and dissemination: This trial has full ethical approval. It will be disseminated via peer reviewed publications and conference presentations. The results will enable clinicians, patients and health service

Strengths and limitations of this study

- To date, Assessing Cognitive behavioural Therapy in Irritable Bowel (ACTIB), when completed, will be the largest trial, worldwide, to address the clinical-effectiveness and cost-effectiveness of cognitive behaviour therapy (CBT) for irritable bowel syndrome (IBS) and has the advantage of comparing a low intensity web-based CBT (WBCBT) with a higher intensity telephone therapist delivered CBT (TCBT).
- ACTIB will recruit from both primary and secondary care, inviting a broad range of patients with refractory IBS from specialist as well as community settings. This will aid generalisability of the findings.
- Owing to the online nature of the Low intensity CBT arm, patients without internet access will be unable to participate. However, internet access in the UK is currently over 75% and those without home access could use public computers (eg, local library).
- Participants aged over 60 years must have had a consultant review to exclude other serious causes of their bowel symptoms in the past 2 years, because colorectal cancer is more common in those over 60 years of age and guidelines recommend that changes in bowel habit in this group require hospital tests beyond the scope of this trial.

planners to make informed decisions regarding the management of IBS with CBT.

Trial registration number: ISRCTN44427879.

INTRODUCTION

IBS is a common chronic gastrointestinal disorder that affects 10–22% of the UK population and costs the National Health Service (NHS) in England over 200 million pounds a year.[1 2] Abdominal pain, bloating and altered bowel habit affect quality of life, social functioning and time off work.[3 4] Treatment commonly relies on a positive diagnosis, reassurance, lifestyle advice and drug therapies. However, the evidence base for commonly used medications such as bulking agents and antispasmodics is limited,[4] and many patients suffer ongoing symptoms.

Face to face cognitive behavioural therapy (CBT) has been shown to be helpful for IBS, reducing IBS symptom severity and improving QOL measures,[5–7] and it has the potential to have long-term benefits, whereas medications are aimed at symptom relief. However, CBT is not currently routinely offered to patients with IBS due to poor availability. Additionally, face to face CBT in this setting was not shown to be cost effective in a Cochrane review[5] and there are problems with limited concordance[5] with face to face therapy. For instance, in the Kennedy trial,[6] fewer than half of the participants were considered to have completed therapy by the end of the intervention and 41% were recorded as declining therapy or dropping out, often due to time issues such as work and child care commitments. Nevertheless, National Institute for Health and Care Excellence (NICE) guidance[4] recommends CBT for patients with refractory IBS symptoms (ie, ongoing symptoms after 12 months despite being offered appropriate medications and lifestyle advice).

A potential approach is to consider web-based CBT for IBS. Web-based CBT has been shown to be helpful for a number of long-term conditions, for example, depression,[8] tinnitus[9] and fatigue in multiple sclerosis,[10] and is recommended in Guidelines for the management of depression.[11] It could be a cost-effective way of providing help to those with IBS. Recent small pilot trials show promise for web-based CBT in IBS,[12–14] but indicate that some therapist input is needed. Web-based delivery has the advantage that it can be accessed at a time and place convenient to the participant, can be undertaken at a pace that suits each individual's circumstances, and does not require extra travel time and costs. The increasing availability of the Internet makes this a good medium to provide easily accessible patient information and self-management programmes. The majority of households in the UK now have web access. This is, therefore, an ideal time to assess and disseminate new web-based interventions. Members of this team have already developed a CBT website to support patients with IBS (Regul8) and trialled it among 135 patients with more than 90% follow-up in the National Institute of Health Research (NIHR)-funded MIBS study.[14] Even with this (underpowered) sample, and very minimal nurse input, Subjects Global Assessment of Relief (SGA) scores (ie, relief from IBS symptoms) and their Enablement Scores (sense of control over their IBS) were significantly improved in the Regul8 groups compared to the non-website group at 3-month follow-up.

This trial comparing the clinical-effectiveness and cost-effectiveness of therapist delivered CBT (TCBT) and a lower intensity therapist supported web-based self-management programme will provide evidence to enable clinicians, patients and health service planners to make informed decisions regarding the management of IBS with CBT.

MAIN RESEARCH QUESTION

What is the clinical-effectiveness and cost-effectiveness of TCBT and web-based CBT (WBCBT) for patients with refractory irritable bowel syndrome?

RESEARCH OBJECTIVES

Primary objectives

1. Estimate the clinical effectiveness of therapist delivered telephone CBT (TCBT) plus treatment as usual (TAU) for reducing the severity and impact of IBS symptoms compared to TAU alone at 12 months after randomisation.
2. Estimate the clinical effectiveness of Regul8, a previously developed web based CBT programme, with minimal therapist support (WBCBT) plus TAU for reducing the severity and impact of IBS symptoms compared to TAU alone at 12 months after randomisation.

Secondary objectives

3. To compare the cost-effectiveness of TCBT and WBCBT in comparison to TAU over the 12-month follow-up period.
4. To estimate (1) and (2) at 3 and 6 months after randomisation.
5. To assess whether TCBT and/or WBCBT have a positive impact on relief of IBS symptoms, quality of life, enablement, anxiety and depression compared to TAU at 3, 6 and 12 months follow-up, and acceptability of the treatment.

Tertiary aims

6. To investigate possible cognitive and behavioural mediators or processes of clinical improvement for both the TCBT and WBCBT.
7. To examine predictors and moderators of outcome.

METHODS AND ANALYSIS

Design

Three arm multicentre randomised controlled trial.

Method

Four hundred and ninety-five patients with refractory IBS will be individually randomised to TCBT+TAU, or

WBCBT (a previously developed self-management CBT website with low levels of therapist support)+TAU, or TAU alone for 9 weeks with 12-month follow-up.

Setting

Treatment will take place at participants' homes via telephone and internet. Therapists will be based at the South London and Maudsley NHS Foundation Trust (SLAM). Participants will be recruited from London and the South Coast of England from primary and secondary care.

Target population

Inclusion Criteria: Adults (18 years and over) with refractory IBS. Refractory IBS is defined for this study as fulfilling the ROME III criteria for IBS[15] and reporting ongoing clinically significant symptoms determined by a IBS symptom severity score (IBS-SSS) of 75 or more. Patients need to have been offered first-line therapies (eg, antispasmodics, antidepressants or fibre based medications) and have continuing IBS symptoms for 12 months or more. Potential participants aged over 60 years will only be included if they have had a consultant review in the previous 2 years to confirm that their symptoms are related to IBS and that other serious bowel conditions have been excluded. This is because there is an increased risk of bowel cancer in the over 60 years' age group and clinical guidance suggests further investigations should be undertaken in this group.[4]

Exclusion criteria: Unexplained rectal bleeding or weight loss, diagnosis of inflammatory bowel disease, coeliac disease, peptic ulcer disease or colorectal carcinoma. People unable to participate in CBT due to speech or language difficulties or those with no access to an internet computer to be able to undertake the WBCBT or who have received CBT for IBS in the past 2 years, and those who have had previous access to the Regul8 website or who are currently participating in an IBS/intervention trial.

Withdrawal criteria: Participants will be withdrawn from the trial if there are any concerns regarding informed consent. Participants can also withdraw if they choose, without giving a reason. If a participant withdraws consent for research follow-up during the trial, the trial team will be informed. Information will be collected in the Drop-out Report Form and, where possible, reason for drop out will be recorded.

Planned interventions

Two methods of delivering CBT are being assessed in this study: TCBT and a lower intensity WBCBT—the Regul8 website with some therapist support.

There are three key differences between the therapy trial arms

1. The use of a CBT self-management patient manual in the TCBT arm versus access to Regul8, an interactive, tailored CBT self-management website[14] for the WBCBT arm.
2. The amount of therapist contact time/intensity of the intervention—TCBT participants will receive a total of 8 h of telephone therapy contact time compared to 2.5 h in WBCBT.
3. The TCBT telephone sessions will be formulation driven and, although based on the content of the sessions/chapters of the patient manual detailed below, order and extent to which these are covered will be individualised. For WBCBT, patients are encouraged to work sequentially through the Regul8 sessions, although the therapist may suggest they focus more on some sessions than on others.

The CBT content of the two treatments is the same and is based on an empirical cognitive behavioural model of IBS.[16] The model specifies that factors such as stress and/or gastric infection trigger the symptoms of IBS, which are then maintained by patients' cognitive, behavioural and emotional responses to the symptoms. For instance, if a patient becomes anxious (emotion) about the symptoms, believes he/she has no control over them (cognitions) and responds by avoiding social situations (behaviour), this can increase anxiety and maintain symptoms through the link between a heightened autonomic nervous system and the enteric nervous system. This model was used to structure the content of the therapy sessions in our Regul8 website for the MIBS pilot study,[14] which, in turn, drew from two efficacious IBS RCTs conducted by members of our research team, a nurse-delivered CBT trial[6] and a trial of a more minimal CBT based self-management programme.[16] The therapy consists of education, behavioural and cognitive techniques, aimed at improving bowel habits, developing stable, healthy eating patterns, addressing unhelpful thoughts, managing stress, reducing symptom focusing and preventing relapse. A summary of the sessions and related homework tasks are presented in table 1.

Participants randomised to TCBT will be contacted by one of the therapist teams to organise the therapist telephone sessions, and will be sent a detailed CBT manual including homework sessions to support the sessions. The TCBT arm will have six 1 h telephone sessions with a CBT therapist over 9 weeks as well as homework tasks. They will also receive two 1 h booster sessions at 4 and 8 months. CBT will be delivered by telephone rather than face to face, as both have similar efficacy,[17] improve accessibility, are efficient and less costly, and can be readily delivered from specialist-centralised services across a large geographic area.[17–19]

Participants randomised to the WBCBT arm will be provided with log-in access to Regul8. They will be advised to start working through the eight online weekly sessions and homework tasks, and will receive weekly automated email reminders. In addition, they will receive three brief 30 min telephone therapy support calls over 9 weeks and two 30 min booster sessions at 4 and 8 months. The telephone CBT sessions for the WBCBT arm are undertaken while they are working

Table 1 Summary of the Self-Management Sessions included in the Regul8 website and the TCBT patient manual

Session 1: Understanding your IBS	Rationale for self-management, which includes the following explanations 1. Possible causes of IBS and illustrative physiology of the digestive system together with the functional changes that occur in the gut as a result of IBS 2. How the autonomic nervous system ('fight-or-flight' stress system) may interact with the enteric nervous system
Session 2: Assessing your symptoms	Self-assessment of the interaction between thoughts, feeling and behaviours, and how these can impact on stress levels and gut symptoms Development of a personal model of IBS that incorporates these elements Homework: Daily diaries of the severity and experience of IBS symptoms, in conjunction with stress levels and eating routines/behaviours
Session 3: Managing symptoms and eating	Review of the symptom diary Behavioural management of the symptoms of diarrhoea and constipation, and common myths in this area, are discussed. Goal setting is explained The importance of healthy, regular eating and not being overly focused on elimination is covered Homework: Goal setting for managing symptoms and regular/healthy eating. Goal setting, monitoring and evaluation continue weekly throughout the programme
Session 4: Exercise and activity	Importance of exercise in symptom management is covered Identifying activity patterns such as resting too much in response to symptoms or an all-or-nothing style of activity is addressed. Homework: Goal setting for regular exercise and managing unhelpful activity patterns if relevant
Session 5: Identifying your thought patterns	Identifying unhelpful thought (negative automatic thoughts) in relation to high personal expectations and IBS symptoms is introduced Link between these thoughts, feelings, behaviours and symptoms is reinforced Homework: Goal setting plus daily thought records of unhelpful thoughts related to personal expectations and patterns of over activity
Session 6: Alternative thoughts	The steps for coming up with alternatives to unhelpful thoughts are covered together with personal examples Homework: Goal setting plus daily thought records including coming up with realistic alternative thoughts
Session 7: Learning to relax, improving sleep, managing stress and emotions	Basic stress management and sleep hygiene are discussed Diaphragmatic breathing, progressive muscle relaxation and guided imagery relaxation, are presented in video and audio formats Identifying common positive and negative emotions, and the participant's current ways of dealing with these New strategies to facilitate expression of emotion as well as coping with negative or difficult emotions are discussed Homework: Goal setting for stress management, good sleep habits and emotional processing
Session 8: Managing flare-ups and the future	The probability of flare-ups is discussed and patients are encouraged to develop achievable, long-term goals, and to continue to employ the skills they have learnt throughout the manual to manage flare-ups and ongoing symptoms

IBS, Irritable bowel syndrome; TCBT, therapist delivered cognitive behavioural therapy.

through the website self-management programme to help engagement with the CBT programme. Participants will also be able to email the therapist regarding queries about the website programme, during the study. Limited therapist input has been included in this condition as several small trials of web-based[12 13] or manual-based[16] CBT for IBS have shown promising results but indicated that therapist input is important to maintain participant engagement. Qualitative interviews with participants from the MIBS[20] study also highlighted the benefit of the telephone support session in improving patient understanding of Regul8.

In both therapy arms, medical questions will not be addressed by the therapists, and participants will be advised to seek medical advice if they have medical queries. Booster sessions are included in both arms to discuss any setbacks and to reinforce positive symptom management.

Secure website pass-wording will ensure non-contamination of treatments. Patients in the TCBT arm will also be requested not to share their manual with others.

Therapists

CBT trained therapists (clinical psychologists or cognitive behavioural nurse therapists) will provide the telephone CBT sessions for the TCBT as well as the WBCBT arms of the study. Each therapist will receive training in both therapy protocols. Competency ratings will be assessed for the first two patients in each active treatment arm using a modified version of the developed rating scale that had previously been used for assessing competency in delivering CBT for fatigue in primary care.[21]

Therapy manuals

A therapy manual has been written and will be used as the basis to train the therapists. It consists of: information and procedures about the trial, background information about IBS, a description of the anatomy and physiology of the bowel, a cognitive behavioural model of IBS, aspects of the therapeutic alliance, sections on ways of engaging the patient and on various cognitive, behavioural and emotional strategies, information on how to utilise supervision and how to overcome difficulties in the treatment process, and a description of the two different approaches, TCBT and WBCBT. The manual also includes protocols for the five telephone support sessions for the Regul8 website, including instructions for the optimum setting for the telephone calls, in other words, a quiet environment without interruptions and keeping prompt-sheets handy for the sessions so that the therapist can check that all the key points are covered.

Therapy training

Therapists will receive two days of training. Prior to the training days, they will be asked to explore the Regul8 website and read the patient manual. Training consists of information about IBS including diagnosis, aetiology and evidence based practice. The IBS CBT treatment model is presented alongside explanations of how the bowel works and how this relates to functional disturbances such as changes in motility and sensitivity in the gut in IBS. Therapists are taught to include predisposing, precipitating and perpetuating factors in their assessment and to use these in a shared conceptualisation with the patient. Obstacles to engagement and strategies for dealing with these are discussed. The specifics of each of the sessions in table 1 are then covered. Finally, therapists receive an overview of trial protocol including recording the timing and length of sessions, any deviations from protocol including sessions missed or drop out, and confidential storage of audiorecordings.

Therapy supervision

Post-training, therapists will receive monthly 1.5 h group supervision with TC, who covers the TCBT, and RMM, who covers the WBCBT. TC and RMM listen to one audiorecording from each therapist, and rate these recordings using the therapist rating scale, prior to supervision.[21] These sessions will be discussed with the group in supervision. Therapists will also have the opportunity to discuss any problem areas or challenging patients. Regular supervision will ensure that the therapists adhere to the protocols in each arm and that the quality of the therapy is maintained.

Treatment fidelity

All telephone therapy sessions will be audiorecorded for the purpose of assessing treatment fidelity. These recordings will be used for supervision during the study and to check fidelity throughout the trial. Supervisers will listen to one TCBT and one WBCBT tape per therapist per month. A subset of the audiorecordings will be analysed by two independent clinicians once the trial has ended. At least two sessions for every therapist (when available) and for therapy type will be rated in terms of adherence to the manual or web-based approach (5 item, 7-point Likert scale). The therapeutic alliance between therapist and participant will also be rated on a seven-point Likert scale used in a previous large RCT of treatments for chronic fatigue syndrome.[22]

Treatment as usual

Patients in all three arms will receive TAU, with the control arm being TAU alone. TAU is defined as continuation of current medications, and usual general practitioner (GP) or consultant follow-up with no psychological therapy for IBS. All GPs or consultants involved in the study will receive a copy of the NICE Guidance for IBS at the start of the study, to ensure all clinicians have standard best practice information on IBS management. They will also receive a Desktop prompt to remind them of the guidelines and inclusion criteria. All participants will receive a standard information sheet on Lifestyle and Diet in IBS, based on the NICE guidance. Information will be collected on any changes in IBS treatments/management during the study, and numbers of GP and consultant consultations will be recorded for all three arms.

The TAU-alone participants will have access to the WBCBT website at the end of the trial follow-up period, but without the therapist support.

Recruitment

Patients will be recruited from secondary and primary care.

We plan to recruit 495 participants over 22 months (23 randomised/month) from GP surgeries in two regions (Southampton and London) and Secondary Care Gastroenterology Clinics in two regions (Southampton and London (GSTT, King's College Hospital)).

Primary care patients will be identified by searching GPs' lists for those with a diagnosis of IBS and by opportunistic recruitment of patients presenting with symptoms consistent with IBS. We will utilise the Clinical Research Network (CRN) to aid recruitment and retention of GP practices. We will include practices with urban and rural settings, and with a range of sociodemographic characteristics. GP practices willing to participate in the study will search their list for adult patients aged 18 years and above with a diagnosis of IBS. Potential participants will be contacted by letter (sent by the GP surgery) informing them about the trial and inviting them to take part. The GPs will check the lists of patients to be contacted prior to the invite letters being sent out to ensure that it is appropriate to contact them. The mailing will include the Assessing Cognitive behavioural Therapy in Irritable Bowel (ACTIB) patient information sheet. Participants who are interested in participating in the study will return a reply slip with their contact details in a prepaid response envelope to the research team. GPs will also be able to opportunistically provide information about the trial to potential recruits during their GP surgeries. Thus, if a patient with IBS attends a GP consultation, GPs will give them the patient information sheet regarding the trial, and the reply slip and envelope. Invite letters will be sent out from the identified GP practices in a stepwise manner over time, and response rates will be monitored to ensure adequate recruitment levels and a steady workload for the therapists.

Secondary care patients will be identified from gastroenterology (GI) clinics. Where available, clinic lists will be searched for patients with a diagnosis of IBS. Potential participants will be contacted by letter (sent from the clinic) informing them about the trial and inviting them to take part. The Consultants will check the lists of patients to be contacted prior to the invite letters being sent out to ensure that it is appropriate to contact them. The mailing will be as for the primary care patients. The consultants will also be able to opportunistically provide information about the trial to potential recruits during their clinics.

Adverts will also be placed in relevant GP and GI clinics and on NHS websites. Clinics and GP practices will have information packs to hand out to potential participants.

Study procedures

Information is also in the Consort diagram (figure 1) and table 2 (screening and data collection).

Those responding to the recruitment invitation letter will be contacted by the study team to complete a screening process consisting of the Rome III criteria, and questions about exclusion and inclusion criteria to check if they fulfil the eligibility criteria for the study. They will be identified with a unique ID number. Any patient indicating they may have a 'red flag' symptom that would indicate the need for further investigations (ie, unexplained weight loss or rectal bleeding) will be referred back to their GP for further assessment and will not enter the study unless the GP feels the symptoms have been fully assessed and that the patient is suitable for study entry.

Those fulfilling the screening entry requirements will be contacted by one of the research team to make sure they are fully informed of trial procedures, and they will be sent the login and access details for the website in order for them to complete an on-line consent form. They will then be sent arrangement details to have a blood test for full blood count, tissue transglutaminase antibodies and C reactive protein (CRP), to exclude alternative diagnoses, such as anaemia that requires further investigation and coeliacs disease (as recommended for IBS diagnosis in the NICE guidelines[4]). The blood tests will be undertaken by practice nurses/GPs within the GP surgeries or by phlebotomists/research nurses at the secondary care sites. Samples will be sent to University Southampton Hospital pathology laboratory for testing and will then be destroyed. The results will be made available to the participants' GP. If the blood tests are within normal limits, the participant can complete the baseline measures and can then be randomised. If the blood tests show an abnormal result, that is, a CRP over the normal laboratory range, anaemia or a positive test for coeliacs disease, the patient will not be randomised to the trial but will be referred back to his or her GP for further assessment.

Randomisation

Randomisation will be provided by an independent randomisation service at the UKCRC registered King's Clinical Trials Unit (CTU) and accessed by study sites via a web-based system. Randomisation will be at the level of the individual, using block randomisation with randomly varying block sizes, stratified by centre (Southampton GP practices, Southampton secondary care, London GP practices, London secondary care). Confirmation emails will be generated automatically and sent to relevant study site and coordination staff.

Blinding

It is not possible in therapy trials to blind participants or therapists to treatment allocation, however, no hypotheses have been proposed as to the superiority of one treatment over the other. As the research assistants are responsible for allocating patients to therapists who have current availability, they will also be unblinded, however, the principal investigators and statisticians will remain blinded. All outcomes are patient reported and collected via the internet, following automated email reminders. The trial team member who will contact

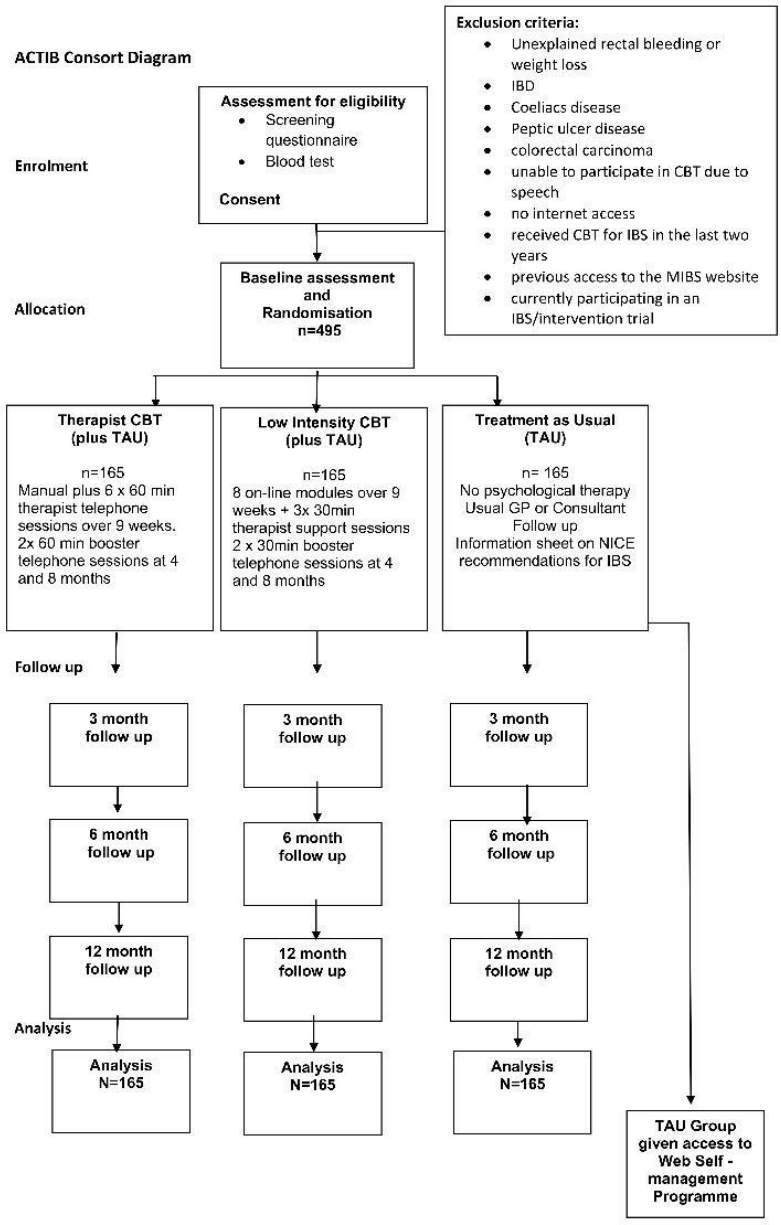

Figure 1 Consort diagram for Assessing Cognitive behavioural Therapy in Irritable Bowel (ACTIB).

participants to capture primary outcome data by telephone on the short questionnaire for those who have not completed follow-up questionnaires after email reminders, will be blinded to the participants treatment group, to avoid bias.

Locked codes will be used for treatment allocation and the trial statisticians will be blinded to treatment allocation, as will be the Data Monitoring and Ethics Committee (DMEC), in order to take actions on the basis of the unblinded data alone. The majority of the data will be analysed blind and the codes only unlocked when necessary, to enable analysis of therapist effects.

Data collection

Research data will be entered onto GCP compliant online data entry systems at CTU (InferMed MACRO) and Regul8 on the LifeGuide Platform. Invite reply data will be entered into the Research Team databases locally. Participant screening data will be collected by telephone and entered into MACRO by the study site staff. Baseline data will be collected prior to randomisation. Baseline and outcome data will be patient self-completed on a separate data collection section of the Regul8 website (as was carried out successfully for the MIBS study), away from the study team, thus avoiding any influence

Table 2 Screening and data collection across the trial: summary of the key trial processes from receipt of the invite reply from the potential participant to the data collection time points

CRF	Completed by	Database	Preconsent	Baseline	3 m	6 m	12 m	Ongoing or during treatment	Ref
Invite reply	P	RT	X						na
Screening Questionnaire	P/TT	M	X						na
Consent	P	R		X					na
Sample requisition form	RN	RT		X					na
Adverse events form	TT	M						X	na
Drop-out event form	TT	M						X	na
Note review form	TT	M					X		na
IBS-SSS	P	R		X	X	X	X		23
WASAS	P	R		X	X	X	X		24
SGA	P	R			X	X	X		25
EQ5D	P	R		X	X	X	X		26
Patient enablement	P	R			X	X	X		27
Hospital Anxiety and Depression Scale	P	R		X	X	X	X		28
Client Service Receipt Inventory	P	R		X	X	X	X		29
Cognitive Scale CG-FBD	P	R		X	X	X	X		30
B-IPQ for IBS	P	R		X	X	X	X		31
IBS Behavioural Responses Questionnaire	P	R		X	X	X	X		32
BES	P	R		X	X	X	X		33
"Impoverished Emotional Experience (IEE)" factor of the Emotional Processing Scale-25	P	R		X	X	X	X		34
PANAS	P	R		X	X	X	X		35
Demographics	P	R		X					na
About your IBS	P	R		X					na
Safety questions	P	R			X	X	X		na
Rating of satisfaction	P	R			X	X	X		22
Thoughts on my treatment	P	R			X	X	X		36
Therapist database	T	MT						X	na

BES, Beliefs about Emotions Scale; B-IPQ, Brief Illness Perception Questionnaire; CG-FBD, Cognitive Scale for Functional Bowel Disoders; CRF, Case Report Form; IBS, Irritable bowel syndrome; IBS-SSS, IBS Symptom Severity Score; M, MACRO Clinical Trials Unit database; MT, MACRO Therapist database; na, not significant; P, patient; PANAS, Positive and Negative Affect Schedule; SGA, Subject's Global Assessment of Relief; R, LifeGuide Regul8; RN, Research Nurse/Phlebotomist; RT, Research Team database; T, therapist; TT, trial team; WASAS, Work & Social Adjustment Scale.

of the study team on the responses and reducing bias. This website will be maintained by the computer support team at Southampton, which is hosting the website. Participants will be given a unique password to log onto the website. Their data will be identified by a unique identification number and will be kept separate from any personal identifying data, to maintain confidentiality. A Therapist database on the CTU MACRO system will be completed by the therapists. It will record which therapist provided the sessions, number of sessions and other contact telephone calls, any drop outs from therapy and a therapist-recorded rating of patient change, adherence and acceptance of therapy model.

Baseline measures

The screening questionnaire will capture baseline data including Rome III questionnaire, duration of IBS, type, previous CBT, medications previously taken for IBS, and inclusion and exclusion criteria. The participant will complete an online baseline assessment questionnaire, which includes the outcome measures detailed below plus sociodemographic details, current medication, medical history and medications, duration of IBS symptoms and previous or current psychiatric diagnoses.

Outcome measures

Outcome data and questionnaires will be completed at baseline, 3, 6 and 12 months after randomisation, by all participants. Participants will be sent a reminder email at 3, 6 and 12 months, to prompt them to complete entering the data 1 week prior to the questionnaire due date. If it has not been completed within 1 week of the reminder, a further two reminders will be sent. One week after that, if no data have been entered, the research team will ring the participant to ask if they can collect the data by hard copy or over the telephone. 90% follow-up was achieved (at 12 weeks) by this method in the MIBS trial, which collected very similar

baseline and outcome measures to those proposed for this study.

Primary outcomes: IBS-SSS and WASAS

IBS Symptom Severity Score (IBS SSS)[23] is widely used in IBS studies. It is a five item self-administered questionnaire measuring: severity of abdominal pain, duration of abdominal pain, abdominal distension/tightness, bowel habit and quality of life. (Maximum score 500: <75 normal bowel function, 75–174 mild IBS, 175–299 moderate IBS, 300–500 severe IBS). A 50 point change from baseline is regarded as clinically significant.[23]

The Work and Social Adjustment Scale (WASAS) measures the effect of the IBS on people's ability to work and manage at home, participate in social and private leisure activities, and maintain relationships.[24] WASAS has been shown to be sensitive to change in IBS trials.[6 16] It has five aspects scored 0 (not affected) to eight (severely affected), total possible score 40.

Secondary outcome measures

Two of the secondary outcomes will not be completed at baseline, only at follow-ups These include the SGA (Subject's Global Assessment of Relief)[25] and the Patient Enablement Questionnaire.[16]

The SGA is frequently used in treatment trials to identify IBS responders to therapy.[25] Participants rate their relief from IBS symptoms on a scale of 1–5 ranging from 'completely relieved' to 'worse'. Scores are dichotomised so that patients scoring from 1 to 3 are considered responders and those scoring 4–5, non-responders.

The Patient Enablement Questionnaire[27] assesses change in the participants' ability to cope with their illness and life after treatment.

Mood will be measured by the Hospital Anxiety and Depression Scale (HADS),[28] a well validated, commonly used, self-report instrument for detecting depression and anxiety in patients with medical illnesses.

The acceptability of the self-management treatment will be assessed using questions where patients rate the overall effectiveness of the programme, the efficacy of programme compared to other treatments they have tried and whether they enjoyed the programme.

The Client Service Receipt Inventory (CSRI)[29] and EQ-5D[26] will be used to gather information on use of health services, and health-related quality of life, respectively. The CSRI has been adapted for use in many economic evaluations and has been used in previous IBS evaluations. The EQ-5D is the most frequently used tool for generating quality-adjusted life years (QALYs), which are favoured by NICE.

Adherence to therapy

Patients' adherence to the treatments will be measured through recording the number of phone sessions and an automated count of web sessions accessed. Completing four or more sessions of the website and one or more of the telephone support calls will be deemed as compliant with the website. In the TCBT arm, completing four or more of the initial telephone CBT sessions will be deemed as compliant.

Any modifications or departures from randomised treatments, and withdrawal of participants from trial treatment or research follow-up, will be recorded and reported as such.

Putative mediator variables

Mediator variables include cognitions and behaviours that form part of the cognitive behavioural treatment model and are targets of the therapies.

These include

Cognitive Scale for Functional Bowel Disoders (CG-FBD),[30] a 31 item scale assessing unhelpful cognitions related to IBS.

Brief Illness Perception Questionnaire for IBS (IPQ),[31] consisting of an eight point scale to assess participants perception of their illness.

The Belief about Emotions Scale (BES),[33] a 12-item questionnaire that measures beliefs about the unacceptability of experiencing and expressing negative emotions. These beliefs are likely to have implications for emotion regulation and processing.

The Irritable Bowel Syndrome-Behavioural Responses Questionnaire,[32] a 26 item scale that measures changes in behaviour specific to managing IBS symptoms.

The "Impoverished Emotional Experience (IEE)" factor of the Emotional Processing Scale,[34] which is composed of five items, and relates to the labelling and awareness of emotional events that influence the way people process their emotions.

The Positive and Negative Affect Schedule (PANAS),[35] which measures both positive and negative affect. The current results indicate that positive and negative effect are relatively independent dimensions. Participants will complete only the positive effect subscale because the HADS scale will already measure negative effect.

GP notes review

Patients' GP notes will be reviewed at 12 months to assess GP and other consultations in the year prior to entering the study and in the 12 months since entry into the study. Other studies have shown an impact on GP contacts from patient self-management programmes.[16 37]

Qualitative component

A nested qualitative study will explore patients' experiences of treatments. The objectives of this study are: to identify factors that facilitate or impede adherence to web-delivered and therapist-delivered CBT; to provide insight into the quantitative results; and to explore social and psychological processes of change. Semistructured interviews will be conducted at 3 and 12 months, with approximately 17–20 participants per arm (ie, 10–12%, sampled purposively to encompass a mix of gender and ages, and a range of baseline symptom severity scores). Interviewers will use topic guides comprising open-

ended questions and prompts designed to elicit participants' accounts of their experiences of IBS in relation to the trial. Interviewing participants from each active arm will enable us to identify factors related to adherence and change processes; including participants from the TAU arm will provide insight into the quantitative results. Interviewing the same participants at 3 and 12 months will allow us greater depth to explore change processes over time and provide the potential to understand better any differences in the quantitative results between 3 and 12 months. Interviews will be transcribed verbatim. Analysis will begin on completion of the first few interviews and will proceed iteratively, thus allowing early insights to be explored more fully in later interviews and topic guides to be modified if necessary. Inductive thematic analysis,[38] employing supplementary techniques from grounded theory,[39] will be used to code the data and to identify themes that capture key concepts and processes. To enhance quality: multiple researchers will contribute, to avoid producing idiosyncratic interpretations; a 'member check' will be conducted whereby interviewees will be invited to comment on summaries of their interviews; and an audit trail (coding manual and notes) and interviewers' field notes will be produced. The qualitative results will thus provide insights into the relative merits of each type of CBT and identify delivery issues to attend to in any future widespread implementation.

Proposed sample size

Sample size was based on the two primary outcomes, IBS-Symptom severity score (IBS-SSS)[23] and WASAS.[24 40]

A 35 point difference between therapy groups and TAU on IBS SSS at 12 months is regarded as clinically significant (assuming a 15 point placebo response in the TAU arm in the trial).[23] Assuming a within-group IBS SSS standard deviation (SD) of 76 points (taken from MIBS pilot study[14]), this equates to an effect size of 0.46. To achieve 90% power to detect such an effect or larger using a two-sided independent samples t test at the 2.5% significance level (adjusting for 2 primary outcomes), would require 119 subjects per group. Based on each of 10 therapists delivering therapy to 17 patients within WBCBT and TCBT groups, and an intraclass correlation of 0.02, taken from Baldwin,[41] this sample size needs to be increased by an inflation factor of 1.32, to take account of therapist effects. We will measure IBS SSS at baseline and assume that baseline values are predictive of post-treatment values (correlation 0.4). Accounting for this in our statistical analysis model allows us to decrease the sample size by a deflation factor of 0.84. Finally, assuming that attrition will be less than 20%, we apply a further inflation factor (factor 1.25) to allow for this. The final sample size requirement is 165 patients per group, or 495 patients in total.

In terms of our second primary outcome (WASAS), this sample size would be sufficient to detect a clinically important difference between the WBCBT (or TCBT) and TAU groups in the WASAS. Specifically, we can assume inflation factors of 1.32 for correlation of outcomes within therapists, and of 1.25 for attrition and a deflation factor of 0.84, for correlation between baseline and follow-up measures. Therefore, a moderate effect size of 0.46 could be found with 90% power at the 2.5% significance level, given 119 participants per group. Assuming a SD of 8.0 (as estimated in a study of CBT for IBS[6]), this would equate to a clinically meaningful treatment difference of 3.7 points on this scale. This is less than the difference of 5.4 points in change of means that was found in a trial of a CBT-based self-management intervention for IBS.[16]

Statistical analysis

The Statistical analysis plan has been approved by the trial steering committee. The aim is to evaluate effectiveness, and all analyses will follow the intention-to-treat principle. Group differences on the primary IBS-SSS outcome will be assessed using a mixed linear regression model for repeated measurements. In this model, IBS-SSS at post-treatment time points (3, 6 and 12 months) will feature as the dependent variable. Explanatory variables will be baseline IBS-SSS, treatment group, IBS symptoms type, stratifier (centre) and time and time by treatment interaction terms to allow for different group differences at the various assessment time points. (The assessment time point of primary interest is 12 months. The modelling provides the treatment effect estimates at the 12 month time point as well as for further post-treatment secondary time points). Correlation between repeated measures of the same participant or between participants, or due to sharing the same therapist, will be allowed for by including subject-varying random intercepts as well as therapist-varying random intercepts for TCBT and WBCBT groups in the mixed models. Mixed models account for missing outcome data under the missing at random assumption. The effect of departures from this assumption will be checked using sensitivity analyses.[42] WASAS scores will be analysed using mixed models in a manner similar to the analysis of IBS-SSS. Secondary outcomes, including Subjects' Global assessment of relief (SGA), EQ-5D, Enablement, HADS, Brief Illness perception Questionnaire (IPQ), Cognitive Scale for Functional Bowel disorders, The Belief about Emotions Scale (BES), The "Impoverished Emotional Experience (IEE)" factor of the Emotional Processing Scale, The Positive and Negative Affect Schedule (PANAS), adverse events (AEs) and healthcare utilisation, are important to measure the wider IBS effects and will be analysed similarly (as appropriate for continuous or dichotomous outcomes). A complier average causal treatment effect will be estimated using instrumental variable methods to assess efficacy if there is appreciable lack of compliance.[43]

Economic evaluation

We will measure costs and assess cost-effectiveness from both a health service and a societal perspective. To calculate the cost of TCBT, the number of sessions with therapists will be recorded and combined with the unit cost of therapist time. The latter will be calculated using information on the salary band of therapists, with additional costs representing capital, overheads, training and qualifications.[44] We will ask therapists to estimate how much time during a typical working week is spent in telephone contact with patients, and combine this with the total cost and total hours worked per week, in order to produce a cost per hour of direct patient contact time. For WBCBT, the number of times therapist support is provided will be recorded and costed in a similar way. The WBCBT development costs will be estimated and apportioned over those using the intervention. Other service use will be measured with a service receipt schedule at baseline (going back 6 months) and at each follow-up (with measurement covering the whole period since the prior interview). The schedule will be based on other questionnaires used in similar research.[29] Services will include primary and secondary healthcare, and medication. Service costs will be generated by combining these data with appropriate unit cost information (eg, NHS Reference Costs,[44] and the British National Formulary) and these costs added to the intervention costs in order to generate total health costs per person.

Societal costs will be calculated by including family care costs and lost production. Family care costs will be recorded by asking patients to state how much time per week family members (and friends) spent providing support in specific areas *because of the IBS*. This time will be combined with average wage rates. Lost days and hours from work will be recorded on the schedule and combined with average wage rates to generate lost production costs. Cost comparisons between the three groups will be made at 3, 6 and 12 months, and over the entire follow-up period, in both cases, controlling for baseline costs. Cost data are usually skewed and cost comparisons will use a bootstrapped regression model to generate appropriate 95% CIs around the cost differences.

Cost-effectiveness will be assessed (from health and societal perspectives) by combining the cost data with the change score on the IBS-SSS, WASAS and QALYs. The latter will be generated from the EQ-5D combined with UK-specific tariffs. Area under the curve methods, controlling for baseline utility, will be used to calculate the number of QALYs accrued over the follow-up period. If outcomes are better for one group compared to another and costs are lower, then it will be defined as being 'dominant'. If outcomes are better and costs are higher, an incremental cost-effectiveness ratio will be generated to indicate the extra cost incurred to achieve an extra point reduction in symptoms or extra QALY. Cost-effectiveness planes will be produced, using 1000 cost and outcome differences (from bootstrapped regression models) for each 2-way comparison, to explore the uncertainty around the results. Cost-effectiveness acceptability curves will also be produced using bootstrapped regression models with net benefit values as the dependent variables. The net benefit approach requires an assumption about the value placed on a unit improvement in outcome. For QALYs, a range from £0 to £60 000 will be used, thus including the threshold thought to influence NICE decisions. For the IBS-SSS and WASAS, there are no accepted thresholds, so a range will be chosen such that the points at which one intervention has a 60%, 70%, 80% and 90% likelihood of being the most cost-effective option can be identified.

Sensitivity analyses will be conducted by changing the intervention costs upwards and downwards by 50%, using minimum wages to value lost production, family care and travel time, and by also using the replacement cost approach to value family care with the cost of a homecare worker used a shadow price.

Modelling beyond the trial period and making comparisons with other interventions is not in the scope of this project.

ETHICS AND DISSEMINATION

Ethical issues

The trial will be conducted in full accordance with current guidelines for ethical research conduct. The study will be performed subject to Research Ethics Committee (REC) approval, including any provisions of Site Specific Assessment (SSA), and local Research and Development (R&D) approval.

The potential benefit to participants from the interventions in this study is a greater understanding of their IBS, an improved ability to manage their condition and possibly reduced symptom severity or impact on their life from their IBS. This may lead to societal benefits such as a reduction in work days lost and reduced use of NHS resources. The risks of undertaking CBT are minimal; undertaking the sessions will require a time commitment on behalf of the participants, and focusing on their IBS symptoms could temporarily worsen the symptoms in the short term. The CBT is provided alongside usual care so the participants will still have access to all usual NHS services. Participants will be fully informed of the trial procedures before entering the study via a Patient Information Sheet, and any questions will be answered by the research team prior to signing the on-line consent form.

Fair access to the study

Participants need to have web access, which could exclude some people who would otherwise like to take part. However, three quarters of households have web access, this figure is rapidly increasing, and those without home access can use public computers (eg, local library).

Participants aged over 60 years are required to have undergone a consultant review to exclude other serious causes of their bowel symptoms in the last 2 years, because colorectal cancer is more common in those aged over 60 years and guidelines recommend that changes in bowel habit in this group require hospital tests beyond the scope of this trial.

To maximise recruitment and to ensure that motivated patients are not excluded from treatments that may help, participants in the TAU-alone group will be given access to the Regul8 website at the end of the trial.

Dissemination

The results of this study will be communicated to participants at study end and disseminated via peer reviewed publications and conference presentations. The results will enable clinicians, patients and health service planners to make informed decisions regarding the management of IBS with CBT.

Service users

IBS patients and the IBS network, a patient self-help group, have been involved in providing feedback for the design of the MIBS[14] trial (in which the Regul8 website used in this study was developed and piloted). Patients were substantially involved in the website design with service users, working through each on-line module during development and providing 'Think Aloud' feedback to inform the design. Participants from the MIBS trial have also provided input and feedback on the proposals for this research. Two participants are now PPI representatives for this study, providing ongoing input (both informal feedback and participating in Trial Steering Committee (TSC) and research meetings) to ensure it addresses issues relevant to users.

Research governance

This study will be conducted in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines, and the Research Governance Framework for Health and Social Care. The University of Southampton is the Sponsor for this study.

A Trial Steering Committee (TSC) will oversee the trial procedures and ensure good conduct of the study; they will meet at least annually. Observers from the HTA will be invited to all TSC meetings.

A Data Monitoring and Ethics Committee (DMEC) will oversee the trial data and ethics, with an independent chair and at least two independent members, and a Patient and Public Involvement Representative, along with the lead investigator (HE), with the support of the TSC. They will meet at least annually.

Regular updates and meetings will ensure good communication. The collaborators will hold meetings at least four times a year. The research assistant will circulate a monthly update to review progress relative to the project plan, highlighting any issues that need to be addressed. Each team member will consult the other team members immediately by email and/or phone on any issues that arise.

Monitoring and audit

The study will be monitored and audited in accordance with Southampton University procedures. All trial related documents will be made available on request for monitoring and audit by the University of Southampton, the relevant REC and other licencing bodies.

Safety

Adverse events

AE are any clinical change, disease or disorder experienced by the participant during their participation in the trial, whether or not considered related to the use of treatments being studied in the trial.

Serious adverse events

An AE is defined as serious (an SAE) if it results in one of the following outcomes

- A life-threatening AE
- In-patient hospitalisation
- A disability/incapacity
- A congenital anomaly/birth defect in the offspring of a subject
- Other medical events requiring intervention to prevent one of the above outcomes.

Serious adverse reactions

A serious adverse reaction (SAR) can be defined as: A SAE considered to be a reaction to one of the supplementary therapies.

Reporting serious adverse events and reactions (SAEs and SARs)

On completion of an SAE, the chief investigator will assess whether the SAE is a SAR or a (SUSAR). A SUSAR is any adverse reaction that is classed as serious and is suspected to be caused by the intervention, and is not expected. If the SAE is classified as a SUSAR, the trial team will report the SUSAR to the EC. For a SUSAR that is fatal or life-threatening, the team, on behalf of the sponsor, has 7 days to report the SUSAR to the EC. For a SUSAR that is not fatal or life-threatening, the team has 15 days to report. The SUSAR is recorded in the participant's medical notes and the participant will be followed up.

Follow-up after AEs

After a SAE or SAR, a decision will be made by the trial team, after advice from the relevant authorities and the participant's GP, as to whether the participant should be withdrawn from either their randomised treatment or from the trial. Arrangements will be made by the trial team for further assessment and management as agreed with the relevant authorities, GP and participant. The investigator will provide the trial team with a 1-month

follow-up report on all SAEs and SARs. Further monthly reports should be provided in the absence of resolution. These reports will be communicated to the TSC, DMEC and MREC, and to the local R&D office. Blank Adverse Event Forms will be distributed to sites that are recruiting, and therapists and patients will be prompted to self-report SAEs in the follow-up questionnaires.

AEs that do not require reporting

Expected AEs include planned/elective hospitalisations, and these will not be collected as SAEs.

Stopping rules

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the Data Monitoring & EC, Trial Steering Committee, Regulatory Authority or EC concerned.

The trial may also be prematurely discontinued due to lack of recruitment or on advice from a Trial Steering Committee (if applicable), who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

Data protection and anonymity

Data will be collected and retained in accordance with the Data Protection Act 1998.

The Data Protection policy of the School of Medicine, Southampton University, will be complied with.

GP participants will be identified from Health Authority lists (these are available in the public domain) and via the CRN.

The responses to questionnaires will be stored in an anonymised form on a password protected university or CTU server. Any anonymised paper questionnaires will be stored in a locked filing cabinet at Primary Medical Care—University of Southampton, or at King's College London.

Storage of records

Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of 10 years following the end of the study.

CONCLUSION

This paper outlines the protocol for the ACTIB study. This study has significant strengths: to date, ACTIB, when completed, will be the largest trial worldwide to address the clinical-effectiveness and cost-effectiveness of CBT for IBS and has the advantage of comparing a low intensity web-based CBT (WBCBT) with a higher intensity telephone delivered CBT (TCBT). Additionally, ACTIB will recruit from both primary and secondary care, inviting a broad range of patients with refractory IBS from specialist as well as community settings. This will aid generalisability of the findings.

The limitations of this study are that due to the online nature of the Low intensity CBT arm, patients without internet access will be unable to participate. However, internet access in the UK is currently over 75% and those without home access can use public computers (eg, local library). Also, participants aged over 60 years are required to have undergone a consultant review to exclude other serious causes of their bowel symptoms in the past 2 years, because colorectal cancer is more common in the those aged over 60 years, and guidelines recommend that changes in bowel habit in this group require hospital tests beyond the scope of this trial.

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Collaborators The ACTIB trial team: Alice Sibelli; Sula Wingassen; Stephanie Hughes.

Contributors All the authors were involved in the design of the study and were co-applicants for funding (except GO—trial manager). HE wrote the first draft of the grant application, is chief investigator, Co-PI, and leads Southampton Centre Recruitment and is on the TAU arm of the trial. RM-M and TC developed the therapy protocols and training included in the trial. RM-M and TC are Co-PIs. RM-M leads on the Website arm. TC leads on the Therapist arm. PMC leads on the Health Economic evaluation. SL leads on statistical analysis. FB leads on the qualitative component. NC and RL (Consultant Gastroenterologists) are clinical expert advisors and will lead GI clinic Recruitment. All the authors read and approved the final manuscript.

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Competing interests None declared.

Ethics approval Berkshire REC 13/SC/0206.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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Appendix I

CV and publications

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Skills Profile

Teaching & Training

- Completed 'Preparing to Teach' course
- Delivered seminars, tutorials and lectures to university students and healthcare professionals
- Completed marking for undergraduate and post graduate students
- Graduate teaching assistant on King's College London Psychology BSc programme

Therapeutic & Behaviour Change Skills

- Facilitated delivery of IAPT interventions for individuals with long term physical conditions
- Teaching Mindfulness to patients & healthcare professionals
- Development of cognitive behavioural manuals for use in Irritable Bowel Syndrome (IBS)
- Developed a therapy manual for therapists delivering Cognitive Behavioural Therapy (CBT) to individuals with IBS
- Completed courses in CBT ran by British Psychological Society

Consultancy

- In collaboration with EU partner organisations, designed and delivered an accredited stress management online programme for health & social care professionals, as commissioned by EU grant
- Collaborated on systematic review of non-pharmacological interventions in intensive care
- Provided empirically informed literature, training and support for newly established charity "A Spell for the Unwell"

Research & Analysis

- Experienced in conducting systematic reviews, utilising literature and journal databases
- Experienced in use of statistical programmes including SPSS, MPlus and AMOS
- Conducted complex statistical analysis including mediation (path analysis), moderation, regressions and latent class analysis

Project Management

- Coordination of trial procedures for a large randomised controlled trial
- Independent coordination of PhD studies and write ups
- Delivery of pilot stress management programme

Communication & Presentation

- Effective communication during meetings, training sessions and presentations with multidisciplinary teams including medical specials, general practitioners, therapists, researchers and statisticians
- Oral and poster presentations at conferences and internal seminars
- Dissemination activities including publication writing, online promotion

and networking

Education & Certifications

PhD in Psychological Medicine *King's College London* *Feb 2014 – Feb 2018*

Part-time PhD investigating cognitive and behavioural factors in IBS, using data on current professional role

Trainee Health Psychologist *King's College London* *Dec 2013 – Nov 2017*

Submitted British Psychological Society & HCPC accredited portfolio of competence (awaiting viva Nov 2017). Includes evidence of the delivery of behaviour change interventions, teaching, consultancy, professional skills and research

Merit in Health Psychology MSc *King's College London* *Sep 2012- Sep 2013*

Thesis project assessed efficacy moderating factors in a pilot trail of Mindfulness Based Cognitive Therapy (MBCT) in progressive multiple sclerosis. Teaching included training in CBT approaches, acceptance and commitment therapy (ACT), motivational interviewing and stress management & research skills

1st class Psychology BSc *University of Leeds* *Sep 2008 – June 2011*

Thesis project assessed effect of ambivalent attitudes in forming intentions and behaviours

Certificate in Good Clinical Practice *National Institute of Health Research* *June 2016*

Accreditation for good clinical practice in the context of health research

Certificate in teaching mindfulness based cognitive therapy *Bangor University* *June 2015*

5 day intensive retreat on delivery of mindfulness based cognitive therapy

Certificate in teaching mindfulness for stress & health *Breathworks* *Nov 2014 – June 2015*

Completed 4 day training course & passed assessed & supervised practice course delivery to individuals with long term conditions recruited from King's College Hospital

Certificates in Cognitive Behavioural Therapy *British Psychological Society* *Nov 2013 – March 2015*

Completed several courses run by the BPS including 'Introduction to CBT', 'socratic questioning', 'interpreting research in CBT', 'running CBT groups', 'Behavioural experiments' & 'Teaching clients to use mindfulness skills'

Professional Appointments & Experience

Researcher ~ *King's College London* *Oct 2013 - present*

Conducting a range of research and clinical activities on the 'Assessing Cognitive Therapy in Irritable Bowel' RCT

Mindfulness Teacher ~ *NHS, public sector & private practice* *Nov 2014 - present*

Delivery of mindfulness teaching and interventions to individuals with long term conditions and healthcare professionals in IAPT, NHS, charity sector and privately

Lecturing & Tutoring	~	*King's College London & NHS*	*Oct 2013 - present*

Delivery of lectures, seminars, training sessions to higher education students & healthcare professionals in the area of health psychology, mental health, CBT, mindfulness & research skills

Research assistant	~	*King's College London*	*Nov 12 – Aug 2013*

Conducted a range of research and clinical activities on the 'Mindfulness in Multiple Sclerosis' pilot study

IAPT intervention facilitator	~	*IAPT*	*Jan 2013 – Jul 2013*

Facilitated and coordinated delivery of mindfulness and psychoeducational interventions to individuals with long term health conditions, depression & anxiety

Marketing Manager	~	*PCM Ltd*	*Jun 2010 – June 2012*
Market Researcher	~	*Zebra Square Market Research*	*Oct 2008 – Dec 2010*

Publications & Conferences

Journal Articles

(1) Windgassen, S., Moss-Morris, R., Goldsmith, K., & Chalder, T (in submission) Key mechanisms of cognitive behavioural therapy in irritable bowel syndrome: the importance of gastrointestinal related cognitions, behaviours and general anxiety. *Behavior Research and Therapy*

(2) Windgassen, S., Moss-Morris, R., Sibelli, A., Everitt, H.E., Goldsmith, K., & Chalder, T (in submission) Cognitive and behavioural differences between irritable bowel syndrome subtypes. *Behavior Therapy*

(3) Windgassen, S., Moss-Morris, R., Goldsmith, K., & Chalder, T (in submission) Behavioural differences between irritable bowel syndrome subtypes and other psychological associations. *Cognitive Behaviour Therapy*

(4) Windgassen, S., Moss-Morris, R., Goldsmith, K., & Chalder, T (accepted) 'The importance of cluster analysis: An example from irritable bowel syndrome. *Journal of Mental Health*

(5) Windgassen, S., Moss-Morris, R., Goldsmith, K., Chilcot, J., Sibelli, A., & Chalder, T. (2017) The Journey Between Brain and Gut: A systematic review of psychological mechanisms of treatment effect in Irritable Bowel Syndrome. *British Journal of Health Psychology.*

(6) Sibelli, A., Chalder, T., Everitt, H., Workman, P., Windgassen, S., & Moss-Morris, R. (2016). A systematic review with meta-analysis of the role of anxiety and depression in irritable bowel syndrome onset. *Psychological medicine*, *46*(15), 3065.

(7) Windgassen, S., Goldsmith, K., Moss-Morris, R., & Chalder, T. (2016). Establishing how psychological therapies work: the importance of mediation analysis. *Journal of Mental Health*

(8) Wade, D. F., Moon, Z., Windgassen, S. S., Harrison, A. M., Morris, L., & Weinman, J. A. (2016). Non-pharmacological interventions to reduce ICU-related psychological distress: a systematic review. *Minerva anestesiologica*, *82*(4), 465-478.

(9) Bogosian, A., Chadwick, P., Windgassen, S., Norton, S., McCrone, P., Mosweu, I. & Moss-Morris, R. (2015). Distress improves after mindfulness training for progressive MS: A pilot randomised trial. *Multiple Sclerosis Journal*, *21*(9), 1184-1194.

(10) Ryan, C., Bergin, M., Titze, S., Ruf, W., Kunz, S., Mazza, R., & Wells, J. S. (2017). Managing the Process of International Collaboration in Online Course Development: A Case-Example Involving Higher Education Institutions in Ireland, Switzerland, Austria, and the United Kingdom. Innovative Higher Education, 1-12.

Therapeutic Manuals

Regul8: A self-management programme for IBS. *Moss-Morris, R., Sibelli, A., Windgassen, S., Didsbury, L., & Chalder, T. Manual for ACTIB trial. Patient manual*

Regul8: A self-management programme for IBS. *Chalder T., Windgassen S., Sibelli A., Burgess M., Moss-Morris R. Therapist manual*

Conferences & Presentations

(1) Oral Presentation: United Kingdom Society for Behavioural Medicine (UKSBM) 2017 Conference, Liverpool

(2) Oral Presentation: British Association of Behavioural and Cognitive Psychotherapy (BABCP) 2017 Conference, Manchester

(3) Poster Presentation: King's College Student Showcase 2017 Event, London

(4) Oral Presentation: 'The Journey Between Brain and Gut: A systematic review of psychological mechanisms of treatment effect in Irritable Bowel Syndrome' Division of Health Psychology & European Health Psychology Society 2016 Conference, Aberdeen

Awards, Prizes & Positions of Responsibility

Co-editor of Healthily Psyched @ Guy's King's College London Blog	ongoing
Peer review of article for Anxiety, Stress & Coping	2017
Winner of Institute of Psychiatry, Psychology & Neuroscience photography competition	2017
Winner of Departmental Bake Off, Health Psychology Department, King's College London	2016
Featured in KCL Department of Psychological Medicine Newsletter for contribution to DELAROSE Project	2015 & 2016
President of Psychology Society, Leeds University	2011/2012
Social Secretary of Psychology Society, Leeds University	2010/2011